



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 9

A. R. Katritzky &  
A. J. Boulton

Advances in  
Heterocyclic  
Chemistry

Volume 9

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Advances in  
HETEROCYCLIC  
CHEMISTRY

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## Preface

The ninth volume of *Advances in Heterocyclic Chemistry* includes surveys of the chemistry of the following groups of heterocyclic compounds: 1,2,5-thiadiazoles (L. M. Weinstock and P. I. Pollack); 1,3,4-thiadiazoles (J. Sandström); pyridazines (M. Tišler and B. Stanovnik); Reissert compounds (F. D. Popp); phenothiazines (C. Bodea and I. Silberg); and pyrrolopyridines (R. E. Willette).

Suggestions are welcomed for contributions to future volumes; they should be in the form of short synopses.

Thanks are due to the Editorial Board, the publisher, and the authors for their cooperation.

A. R. KATRITZKY  
A. J. BOULTON

*Norwich, England*  
*February, 1968*

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# Reissert Compounds

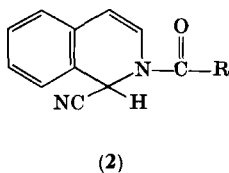
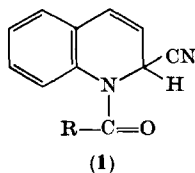
F. D. POPP

*Clarkson College of Technology, Potsdam, New York*

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## I. Introduction

The chemistry of *N*-acyldihydroquinaldonitriles (**1**) and *N*-acyldihydroisoquinaldonitriles (**2**) (Reissert compounds) was the subject of an excellent review in 1955.<sup>1</sup> The purpose of the present



review is to summarize the results since that date. The same general format that was followed in the previous review<sup>1</sup> will be used, as far as possible, in the present one. The literature is covered from the previous review up to August 1967.

<sup>1</sup> W. E. McEwen and R. L. Cobb, *Chem. Rev.* **55**, 511 (1955).



## II. Preparation

A valuable dimension was added to Reissert compound chemistry with the discovery of the methylene chloride–water solvent system for their preparation.<sup>2, 3</sup>

### A. PREPARATION IN AQUEOUS MEDIA

Although several new<sup>4, 5</sup> Reissert compounds were prepared by this method<sup>1</sup> it has been largely displaced by the methylene chloride–water system. The disadvantages of the aqueous method have been discussed.<sup>4</sup>

### B. PREPARATION IN NONAQUEOUS MEDIA

Although solvents such as dimethylformamide<sup>5</sup> have been tried, the use of anhydrous benzene and anhydrous hydrogen cyanide<sup>1</sup> appears to remain as the most general nonaqueous solvent system and several new Reissert compounds have been prepared by this method.<sup>6–8</sup> With the use of anhydrous hydrogen cyanide this method suffers from an obvious disadvantage.

### C. PREPARATION IN METHYLENE CHLORIDE–WATER

An extremely convenient and general<sup>2–4, 9–11</sup> method of Reissert compound formation has been developed. This involves the addition of the acid halide (or less frequently anhydride) neat or in methylene chloride to a mixture of the heterocyclic base in methylene chloride and potassium cyanide in a minimum of water. Although the methylene chloride–water system is heterogeneous it has the advantage over the aqueous system that all the reactants and products are soluble in one phase or the other. Also water is slightly soluble in methylene chloride. The amount of water present is not sufficient to prevent the use of even reactive acid chlorides.<sup>10</sup> This system appears to be the method of choice for Reissert compound formation.

<sup>2</sup> F. D. Popp and W. Blount, *Chem. & Ind. (London)*, 550 (1961).

<sup>3</sup> F. D. Popp, W. Blount, and A. Soto, *Chem. & Ind. (London)*, 1022 (1962).

<sup>4</sup> F. D. Popp, W. Blount, and P. Melvin, *J. Org. Chem.* **26**, 4930 (1961).

<sup>5</sup> I. W. Elliott, Jr., *J. Am. Chem. Soc.* **77**, 4408 (1955).

<sup>6</sup> H. Shirai and N. Oda, *Chem. & Pharm. Bull. (Tokyo)* **8**, 744 (1960).

<sup>7</sup> E. Cuingnet and M. Adalberon, *Compt. Rend.* **255**, 3053 (1964).

<sup>8</sup> F. D. Popp and W. E. McEwen, *J. Am. Chem. Soc.* **79**, 3773 (1957).

<sup>9</sup> F. D. Popp and W. Blount, *J. Org. Chem.* **27**, 297 (1962).

<sup>10</sup> F. D. Popp and A. Soto, *J. Chem. Soc.*, 1760 (1963).

<sup>11</sup> F. D. Popp and J. Wefer, *Chem. Commun.*, 59 (1967).

#### D. EFFECT OF STRUCTURE ON REACTIVITY OF THE HETEROCYCLIC AMINE

The failure of pyridine and acridine to yield Reissert compounds has already been discussed.<sup>1</sup> Although many of the arguments advanced<sup>1</sup> for the failure of pyridine to yield a Reissert compound suffer from the fact that analogous compounds have been prepared from pyridine, no one yet appears to have found the proper conditions for formation of a pyridine Reissert compound.

##### 1. *Quinolines*

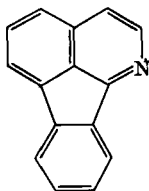
The previous review<sup>1</sup> noted the formation of Reissert compounds from less than half the quinolines investigated and stated that "... the ease of formation of Reissert compounds is dependent upon steric as well as electronic factors, since the presence of substituents in the 2- and 8-positions of quinoline inhibits the formation of ..." Reissert compounds. That a steric factor does indeed exist is evidenced by the fact that from a total of seven 2-substituted and nine 8-substituted quinolines subjected to the reaction none has yielded a Reissert compound.<sup>1, 4</sup> Using the methylene chloride-water solvent system, however, Reissert compounds have been prepared from 3-, 4-, 5-, 6-, and 7-substituted quinolines and from disubstituted quinolines.<sup>4</sup> Quinolines having various substituents in these positions, including all those previously reported as not giving Reissert compounds, gave positive results in this solvent system.<sup>4</sup> In addition to Reissert compound formation, hydroxyquinolines were esterified and aminoquinolines were converted to the amides.

The yields of Reissert compounds with substituents on the quinoline ring vary with the electronic character of the substituent, quinolines with electron-donating groups generally giving the highest yields and those with electron-withdrawing groups the lowest yields. This result has been rationalized in two ways.<sup>4</sup>

##### 2. *Isoquinolines*

Although the number and variety of isoquinolines investigated does not approach that of the quinoline series, it would appear that the synthesis of isoquinoline Reissert compounds is general when the methylene chloride-water solvent system is used.<sup>9</sup> A possible exception is 1-substituted isoquinolines where a steric effect, similar to that

in the quinoline series, may exist. 1-Methylisoquinoline failed to give a Reissert compound although 2-azafluoranthene (**3**), benzoyl chloride, and potassium cyanide gave a material which had the correct



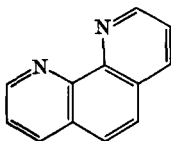
(3)

elemental analysis for a Reissert compound.<sup>9</sup> It should be noted, however, that the compound derived from **3** did not give benzaldehyde on acid-catalyzed hydrolysis.<sup>12</sup> Such a reaction is generally typical for a Reissert compound.<sup>1</sup>

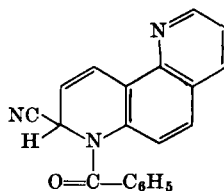
### 3. Diazaheterocyclic Compounds

Except for the formation of a mono Reissert compound from 2,3'-biquinoline and a di-Reissert compound from 6,6'-biquinoline<sup>1</sup> relatively little had been done on diaza systems until recent years.

*o*-Phenanthroline (**4**) does not give a Reissert compound<sup>13, 14</sup> while *m*-phenanthroline gives the mono-Reissert compound (**5**).<sup>13</sup> Neither



(4)



(5)

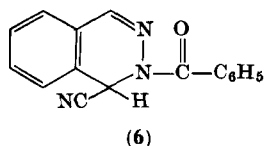
of these results is surprising if one considers that 8-substituted quinolines do not form Reissert compounds.

Phthalazine has been reported to give the compound **6** which, as noted in subsequent sections, behaves as a normal Reissert compound on acid-catalyzed hydrolysis and alkylation.<sup>11</sup>

<sup>12</sup> W. Blount, J. Wefer, and F. D. Popp, unpublished observations (1961, 1966).

<sup>13</sup> F. D. Popp, unpublished results (1962-1963) (presented at 19th Intern. Congr. Pure Appl. Chem., London, 1963).

<sup>14</sup> E. J. Corey, A. L. Borror, and T. Foglia, *J. Org. Chem.* **30**, 288 (1965).



Much further study is needed on the extension of this class of compounds to the diazaheterocyclic area.

#### E. REACTIVITY OF THE ACID CHLORIDE

Until the advent of the methylene chloride–water solvent system the less reactive acid chlorides could be used in the aqueous method but the more reactive acid chlorides required the anhydrous hydrogen cyanide method.<sup>1</sup> This latter method is still sometimes used<sup>6, 8</sup> and in fact has been used with quinoline and the 2- and 3-carboxylic acid chlorides of methylcyclopentadienyl manganese tricarbonyl.<sup>7</sup>

The methylene chloride–water method<sup>3</sup> has demonstrated a wide range of utility and aromatic, aliphatic, cyclic, and diacid chlorides have been used to give the appropriate Reissert compound.<sup>10</sup> It is of interest to note that despite the presence of water in the system it can be used successfully with even aliphatic acid chlorides.

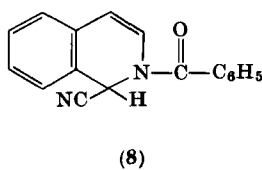
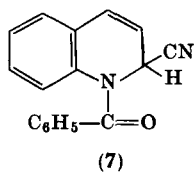
The acid bromide or acid anhydride may be used in place of the acid chloride but the yields of Reissert compounds are generally not as satisfactory with these reagents.<sup>10</sup>

### III. Chemical Properties and Reactions

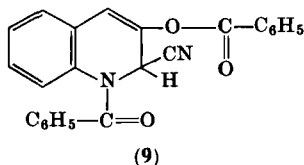
#### A. ACID-CATALYZED HYDROLYSIS

In the early work on Reissert compounds<sup>1</sup> the reaction that attracted the greatest attention was the acid-catalyzed hydrolysis to aldehydes plus the corresponding heterocyclic carboxylic acid or acid derivative.

##### 1. Scope



A wide variety of *N*-benzoyl-1,2-dihydroquinaldonitriles (7) and *N*-benzoyl-1,2-dihydroisoquinaldonitriles (8) with various ring substituents were subjected to hydrolysis with hydrochloric acid in the presence of 2,4-dinitrophenylhydrazine to give, with the exceptions

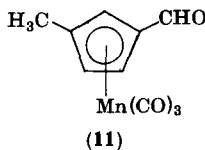
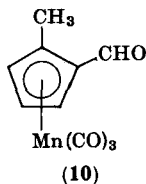


noted below, high yields of benzaldehyde-2,4-dinitrophenylhydrazone.<sup>4, 9</sup> The Reissert compound (9) from 3-hydroxyquinoline failed to yield benzaldehyde.<sup>4</sup> The proximity of the carbonyl function in the 3-position of the Reissert compound (9) to the cyano group may interfere with the interaction of the cyano group and the carbonyl function in the 1-position which is necessary, as indicated in the next section, for the hydrolysis to an aldehyde. The nitro-substituted Reissert compounds such as those from 5-, 6-, and 7-nitroquinoline and from 5- and 8-nitroisoquinoline gave very low yields of benzaldehyde on acid-catalyzed hydrolysis.<sup>4, 9</sup> A somewhat higher yield was obtained from 5- and 8-nitro-3-methylisoquinoline<sup>9</sup> indicating a possible electronic effect. For unexplained reasons the Reissert compounds derived from disubstituted quinolines generally gave lower yields of benzaldehyde than those from monosubstituted quinolines.<sup>4</sup>

Under similar conditions of hydrolysis the phthalazine Reissert compound (6) gave a near quantitative yield of benzaldehyde-2,4-dinitrophenylhydrazone.<sup>11</sup>

A group of Reissert compounds containing various *N*-acyl groups were subjected to hydrolysis under similar conditions to give the aldehyde-2,4-dinitrophenylhydrazone.<sup>8, 10</sup>

Although the synthetic utility of this as a method of aldehyde synthesis has been largely displaced by new techniques, some reports

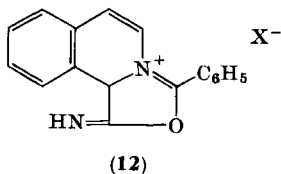


of its use continue to appear. 2-Nitro-5-methoxybenzaldehyde has been prepared in 62 % overall yield from the corresponding acid<sup>6</sup> and the aldehydes **10** and **11** have been obtained from the corresponding acids<sup>7</sup> by making use of Reissert compound formation and hydrolysis. The acid hydrolysis of Reissert compounds has been utilized for the preparation of deuterium-labeled aldehydes.<sup>14a</sup>

The acid-catalyzed hydrolysis continues to be used as a highly satisfactory method for the synthesis of quinaldic acids. The reaction of Reissert compound (**7**) with hydrobromic acid in acetic acid gave near quantitative yields of quinaldic acid hydrobromide with no contamination from other acid derivatives<sup>15</sup> and would appear to be the method of choice for this conversion. This method has subsequently been used to produce high yields of benzo(*f*)quinoline-3-carboxylic acid<sup>16</sup> and phthalazine-1-carboxylic acid.<sup>11</sup>

## 2. Studies of the Mechanism

A reasonable mechanism has been proposed for this somewhat unusual hydrolysis<sup>1, 17</sup> and the isolation of a hydrobromide analog of one of the proposed cyclic intermediates<sup>17</sup> has been reported.<sup>18</sup> This



intermediate (**12**) may be crystallized from hot alcohol and does not decompose on treatment with hot or cold water. Upon decomposition it gives benzaldehyde, isoquinaldamide hydrobromide, and isoquinaldic acid hydrobromide.<sup>18</sup> An impure intermediate had previously been isolated from the acid hydrolysis of another Reissert compound.<sup>8</sup> The reduction of **12** which is discussed in Section III, C confirms structure **12**.<sup>19</sup>

<sup>14a</sup> M. Wahren, *Abhandl. Deut. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.* **1964** (7), 687 (1963); *Chem. Abstr.* **66**, 3564 (1967).

<sup>15</sup> J. W. Davis, Jr., *J. Org. Chem.* **24**, 1691 (1959).

<sup>16</sup> F. D. Popp and W. R. Schleigh, *J. Heterocyclic Chem.* **1**, 107 (1964).

<sup>17</sup> R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.* **77**, 5042 (1955).

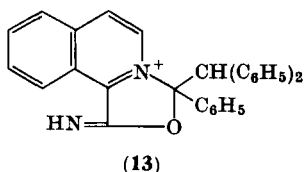
<sup>18</sup> J. W. Davis, Jr., *J. Org. Chem.* **25**, 376 (1960).

<sup>19</sup> I. W. Elliott and J. O. Leflore, *J. Org. Chem.* **28**, 3181 (1963).

### 3. Acid-Catalyzed Condensations

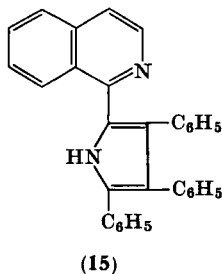
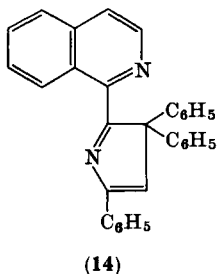
On the basis of the mechanism for the acid-catalyzed hydrolysis of Reissert compounds<sup>1, 17</sup> it can be reasoned that such compounds might function as acylating agents towards carbonium ions. Studies toward this end have been reported.<sup>20-23</sup>

Treatment of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**8**) with benzhydryl and concentrated sulfuric acid in dioxan solution gave isoquinaldamide bisulfate and  $\alpha,\alpha$ -diphenylacetophenone.<sup>20</sup> These results can be explained by the acid-catalyzed conversion of **8** to **12**



followed by deprotonation of **12** and condensation with the benzhydryl cation to give **13**. Addition of water to **13** affords an intermediate which can rearrange to give the observed products.<sup>20</sup>

The sulfuric acid-catalyzed condensation of Reissert compound (**8**) with 1,1-diphenylethylene gave a mixture of 2-(1-isoquinolyl)-3,3,5-triphenylpyrrolenine (**14**), 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**15**), and isoquinaldamide.<sup>20-22</sup> The course of this reaction was studied by carbonyl-<sup>14</sup>C labeled **8** with unlabeled 1,1-diphenylethylene, as



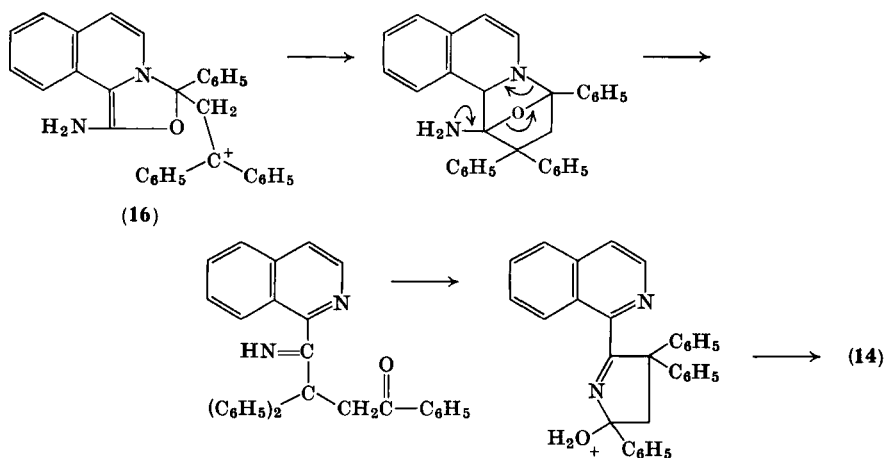
<sup>20</sup> T. K. Liao and W. E. McEwen, *J. Org. Chem.* **26**, 5257 (1961).

<sup>21</sup> T. Y. Yee, W. E. McEwen, and A. P. Wolff, *Tetrahedron Letters*, 3115 (1965).

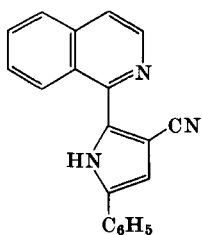
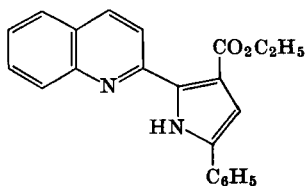
<sup>22</sup> W. E. McEwen, T. Y. Yee, T. K. Liao, and A. P. Wolff, *J. Org. Chem.* **32**, 1947 (1967).

<sup>23</sup> E. K. Evangelidou and W. E. McEwen, *J. Org. Chem.* **31**, 4110 (1966).

well as by reaction of unlabeled **8** with methylene- $^{14}\text{C}$  labeled 1,1-diphenylethylene.<sup>21, 22</sup> These tracer studies as well as other evidence established the structures. The product **15** arose through a rearrangement of **14** and the formation of **14** can be explained by the attack of the conjugate acid (**12**) on 1,1-diphenylethylene to give **16** which can then proceed as shown to **14**.<sup>21, 22</sup>



The acid-catalyzed condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**8**) with acrylonitrile afforded 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (**17**),<sup>23</sup> while ethyl 2-(2-quinolyl)-5-phenylpyrrole-3-carboxylate (**18**) is produced by the acid-catalyzed condensation of 1-benzoyl-1,2-dihydroquinaldonitrile (**7**) with ethyl

**(17)****(18)**

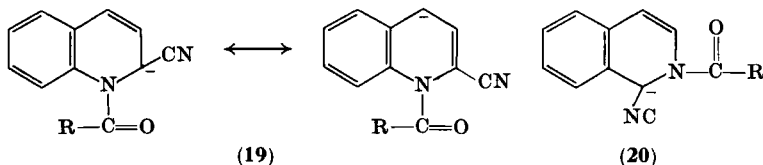
acrylate.<sup>24</sup> These reactions can also be explained by involving the intermediate originally proposed in the acid-catalyzed hydrolysis of Reissert compounds.

<sup>24</sup> W. E. McEwen, private communication (1966).



## B. REACTIONS INVOLVING THE FORMATION OF AN ANION OF THE REISSERT COMPOUND

A number of alkylation reactions, Michael-type additions, and base-catalyzed rearrangements have been previously reported for Reissert compounds.<sup>1</sup> These reactions appear to proceed through the conjugate



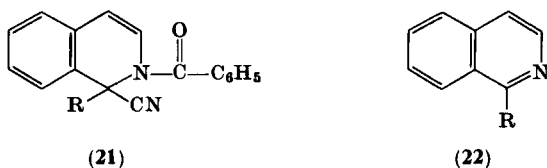
bases **19** and **20**. As noted below reactions of this type appear to be the method of choice for the synthesis of various quinoline and isoquinoline derivatives, particularly the isoquinoline alkaloids.

### 1. Preparation of the Anion

The anion **19** or **20** has most generally been prepared by removal of the hydrogen bonded to a carbon  $\alpha$  to the cyano group by a base such as phenyllithium in ether-dioxan at  $-10$  to  $-20^\circ$  or by a base such as sodium hydride at the temperature of refluxing xylene.<sup>1</sup> Recent work, however, has shown that these anions can be generated and caused to react at room temperature by use of sodium hydride in dimethylformamide.<sup>25-27</sup>

### 2. Reactions with Alkyl Halides

The alkylation of **20**, obtained by the action of phenyllithium on the Reissert compound, with a number of alkyl halides to give **21** which can



then be hydrolyzed to **22** has been discussed.<sup>1</sup> The use of sodium hydride in dimethylformamide at room temperature<sup>25</sup> greatly

<sup>25</sup> F. D. Popp and J. M. Wefer, *Chem. Commun.*, 207 (1966).

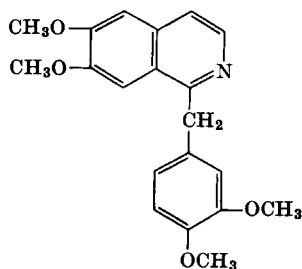
<sup>26</sup> J. R. Kershaw and B. C. Uff, *Chem. Commun.*, 331 (1966).

<sup>27</sup> F. D. Popp and J. M. Wefer, *J. Heterocyclic Chem.* **4**, 183 (1967).

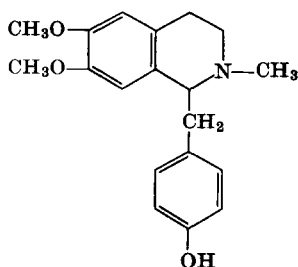
increases the utility of this reaction and it now appears to be the method of choice for the synthesis of 1-alkylisoquinolines.<sup>26, 27</sup>

A new synthesis of aporphines has appeared.<sup>27a</sup> The key step in this synthesis involves the generation of 1-(*o*-nitrobenzyl)isoquinoline by reaction of a Reissert compound with *o*-nitrobenzyl chloride in dimethylformamide in the presence of sodium hydride.

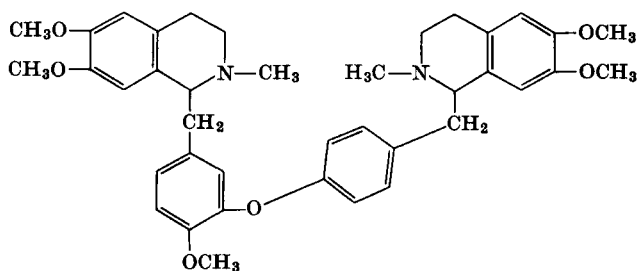
Several additional examples of the alkylation of Reissert compounds appeared before the development of this new system and these are noted below. In addition to the previously reported<sup>1</sup> 1-( $\beta$ -dimethylaminoethyl)isoquinoline the alkylation of **20** with  $\beta$ -chloroethyl-dimethylamine also gave rise to 1,2-di-(1'-isoquinolyl)ethane.<sup>28</sup>



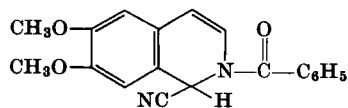
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(25)



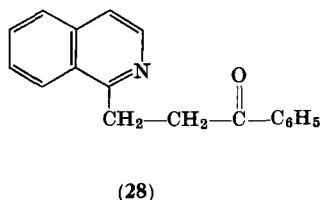
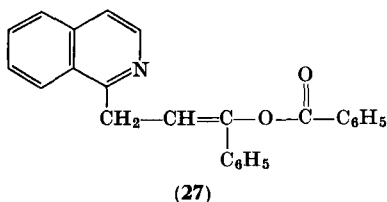
(26)

<sup>27a</sup> J. L. Neumeyer, B. R. Neustadt, and J. W. Weintraub, *Tetrahedron Letters*, 3107 (1967).

<sup>28</sup> V. Boekelheide and A. L. Sieg, *J. Am. Chem. Soc.* **77**, 3128 (1955).

The alkaloids papaverine (**23**),<sup>8</sup> armepavine (**24**),<sup>29</sup> and *O*-methyldauricine (**25**)<sup>30</sup> have been synthesized by making use of the reaction of the anion of 6,7-dimethoxy-2-benzoyl-1,2-dihydroisoquinaldonitrile (**26**) with the appropriate alkyl halide as the key step. It might be noted that this route to the alkaloids was not as useful as the one noted below involving the reaction of aldehydes with the anion of **26**, however, with the advent of the sodium hydride–dimethylformamide room-temperature method<sup>25</sup> it may be that the alkyl halide route could become the method of choice.

The report<sup>1</sup> that alkylation of **19** with methyl iodide occurs in the 4-position rather than the 2-position has been confirmed by vapor phase chromatography.<sup>31</sup>



Reaction of **20** with  $\beta$ -bromopropiophenone using the sodium hydride–dimethylformamide method afforded an intermediate believed to be **27** which was hydrolyzed to the expected **28**.<sup>32</sup>

Alkylation of the phthalazine Reissert compound (**6**) with methyl iodide proceeded normally to give 1-methylphthalazine.<sup>11</sup>

### 3. Reactions with Aldehydes and Ketones

The anions of Reissert compounds **19** and **20** undergo reaction with aldehydes to form esters of secondary alcohols containing the 2-quinolyl or 1-isoquinolyl group bonded to the carbinol carbon atom.<sup>33</sup> Thus benzaldehyde, 1-benzoyl-1,2-dihydroquinaldonitrile (**7**), and phenyllithium in ether-dioxan at  $-10^\circ$  gave **29**,<sup>33</sup> and benzaldehyde, 2-benzoyl-1,2-dihydroisoquinaldonitrile (**8**), and phenyllithium in ether-dioxan at  $-10^\circ$ <sup>33</sup> (or sodium hydride in refluxing

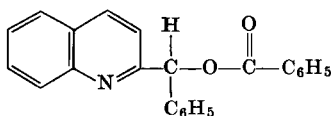
<sup>29</sup> H. W. Gibson, F. D. Popp, and A. C. Noble, *J. Heterocyclic Chem.* **3**, 99 (1966).

<sup>30</sup> F. D. Popp, H. W. Gibson, and A. C. Noble, *J. Org. Chem.* **31**, 2296 (1966).

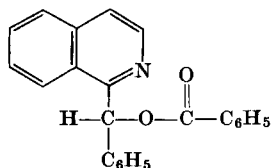
<sup>31</sup> J. M. Wefer, Ph.D. Dissertation, Clarkson College of Technology (1967).

<sup>32</sup> J. M. Wefer and F. D. Popp, *J. Org. Chem.* **32**, 1999 (1967).

<sup>33</sup> L. R. Walters, N. T. Iyer, and W. E. McEwen, *J. Am. Chem. Soc.* **80**, 1177 (1958).

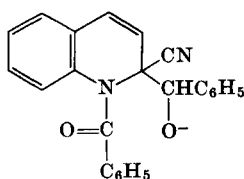


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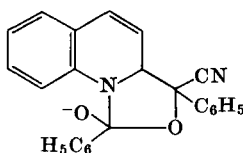


(30)

benzene<sup>34</sup> or sodium hydride in dimethylformamide at room temperature<sup>27</sup>) gave **30**. There can be little doubt that the mechanism of formation of **29** involves an initial formation of **31** which then



(31)



(32)

gives **32** which can undergo elimination-rearrangement to the product.<sup>33</sup> A similar mechanism can be used for the formation of **30**. It is of interest to note that in this case reaction of the anion (**19**) of the quinoline Reissert compound takes place in the 2-position. A wide variety of aldehydes<sup>8, 29, 30, 33-39</sup> ranging from formaldehyde<sup>36</sup> to dialdehydes<sup>30, 37</sup> have been used. The presence of a strongly electron-donating group ( $-\text{N}(\text{CH}_3)_2$ ,  $-\text{OH}$ ) in the *p*-position of benzaldehyde causes the yield to drop to zero.<sup>33, 35</sup> In the case of *p*-hydroxybenzaldehyde this difficulty can be overcome by conversion of the hydroxy group to a benzyloxy group.<sup>35</sup> Steric and electronic factors seem to show up more clearly in the isoquinoline series than in the quinoline case.<sup>33</sup>

The condensation of the anion of **26** with the appropriate aldehyde has played an important part in the convenient synthesis of a number of alkaloids and alkaloid-related materials such as calycotomine (**33**),<sup>38</sup> papaverinol (**34**),<sup>8</sup> armepavine (**24**),<sup>29</sup> and *O*-methyldauricine

<sup>34</sup> H. W. Gibson and F. D. Popp, *J. Chem. Soc., C, Org.*, 1860 (1966).

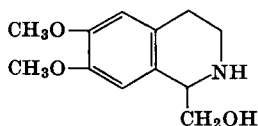
<sup>35</sup> F. D. Popp and H. W. Gibson, *J. Heterocyclic Chem.* **1**, 51 (1964).

<sup>36</sup> L. R. Walters, I. C. Mineo, and R. S. Kripowicz, *J. Org. Chem.* **29**, 980 (1964).

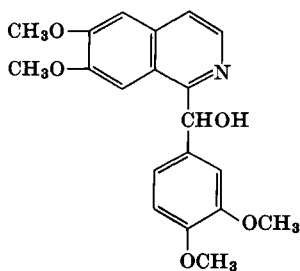
<sup>37</sup> E. G. Podrebarac and W. E. McEwen, *J. Org. Chem.* **26**, 1165 (1961).

<sup>38</sup> H. W. Gibson, F. D. Popp, and A. Catala, *J. Heterocyclic Chem.* **1**, 251 (1964).

<sup>39</sup> F. D. Popp and W. E. McEwen, *J. Am. Chem. Soc.* **80**, 1181 (1958).



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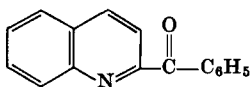
(25)<sup>30</sup> as well as in approaches to the synthesis of emetine.<sup>39</sup> In the case of the synthesis of **24** and **25** it might be noted that the use of the aldehyde sequence gave better yields than the use of the alkyl halide sequence noted above.<sup>29, 30</sup> This advantage was noted despite the need of additional synthetic steps to convert the carbinol ester to a methylene group.<sup>34</sup>

In addition to the use of a dialdehyde to react with 2 moles of Reissert compound in the synthesis of **25**,<sup>30</sup> terephthalaldehyde has been reacted with **19** and **20** to give the meso form and racemate of the bis diol esters.<sup>37</sup> In the quinoline series the product has been converted to a compound having curariform activity.

Although the data are limited, there is sufficient evidence available to show that the condensation of ketones with Reissert anions is a relatively unsatisfactory reaction.<sup>33</sup> It should be pointed out, however, that the expected tertiary alcohols are available by reaction of Grignard reagents with Reissert compounds as noted below.

#### 4. Rearrangements

Rearrangement of the Reissert anions **19** and **20** has been reported to occur in refluxing xylene to give a ketone or in the presence of a



(35)

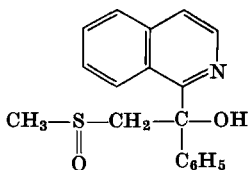


(36)

Grignard reagent to give a tertiary alcohol.<sup>1</sup> Thus **19**, ( $R = C_6H_5$ ) could give rise to **35** or **36** ( $R$  from  $RMgX$ ).

The mechanism of this reaction was shown to be intramolecular by  $^{14}\text{C}$  studies<sup>1</sup> and the details of this work have appeared<sup>40</sup> together with an extension of its scope.<sup>40, 41</sup> A wide variety of tertiary carbinols containing the 2-quinolyl or 1-isoquinolyl group as one of the substituents bonded to the carbinol carbon have thus been prepared. The initial reaction is one between the Reissert compound and  $\text{RMgX}$ , present in the solid phase of the reaction mixture, to give intramolecularly<sup>40</sup> a 1-acylisoquinoline or a 2-acylquinoline. This  $\alpha$ -acyl heterocyclic derivative can undergo further reaction to form a salt of the carbinol either with  $\text{R}_2\text{Mg}$  in solution or with  $\text{RMgX}$  in the solid phase.<sup>41</sup>

It has recently been found<sup>25, 27</sup> that the rearrangement of **19** and **20** to 2-acylquinolines, such as **35**, and 1-acylisoquinolines can be conveniently carried out in dimethylformamide at room temperature. A number of quinolyl and isoquinolyl ketones have been prepared in this manner.<sup>27, 30</sup> Use of dimethylsulfoxide as solvent also allows rearrangement to proceed at room temperature but the initially formed ketones reacted further with the solvent anion to give products such as **37**.<sup>27</sup>



(37)

In a few cases rearrangement is accompanied by or superseded by formation of an isoquinaldonitrile.<sup>8, 42, 43</sup>

### 5. Reactions with Other Electrophiles

*a. Isocyanates.* *O*-Benzoyl-*N*-phenylisoquinaldamide (**38**) and *O*-benzoyl-*N*-( $\alpha$ -naphthyl)isoquinaldamine have been prepared by the reaction of phenyl and 1-naphthylisocyanate, respectively, with the

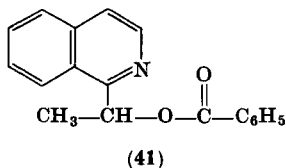
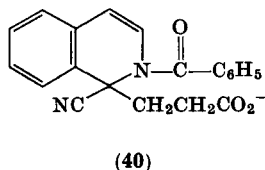
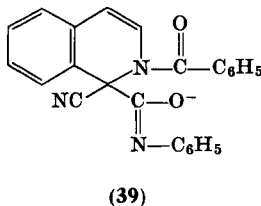
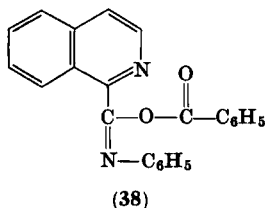
<sup>40</sup> A. P. Wolff, W. E. McEwen, and R. H. Glazier, *J. Am. Chem. Soc.* **78**, 861 (1956).

<sup>41</sup> N. C. Rose and W. E. McEwen, *J. Org. Chem.* **23**, 337 (1958).

<sup>42</sup> H. W. Gibson, Ph.D. Dissertation, Clarkson College of Technology (1965).

<sup>43</sup> J. M. Wefer, A. Catala, and F. D. Popp, *J. Org. Chem.* **30**, 3075 (1965).

anion (**20**) of 2-benzoyl-1,2-dihydroisoquinaldonitrile.<sup>44</sup> There was no analogous reaction between isocyanates and the anion (**19**) of 1-benzoyl-1,2-dihydroquinaldonitrile.<sup>44</sup> The formation of **38** undoubtedly involves an initial addition of **20** to the carbonyl carbon



atom of phenyl isocyanate to form **39** which then gives **38** via a cyclic intermediate in common with other similar reactions of Reissert compounds.

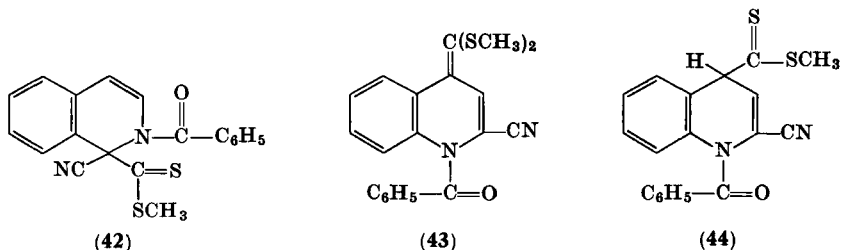
*b. Lactones.* Reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**8**) with  $\beta$ -propiolactone and sodium hydride in dimethylformamide led to the formation of  $\beta$ -(1-isoquinolyl)ethyl phenyl ketone (**28**).<sup>32</sup> Formation of **28** can be rationalized by attack of **20** on the lactone to give **40** which then gives **28** via a cyclic intermediate and decarboxylation.

Reaction of **8** with  $\beta$ -butyrolactone did not produce a simple homolog of **28** but rather methyl-1-isoquinolyl carbonyl benzoate (**41**).<sup>32</sup> It may be that **41** is formed from acetaldehyde generated *in situ*.

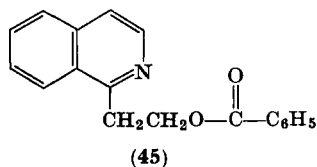
Under similar conditions a number of  $\gamma$ -lactones failed to react. Using phenyllithium in ether-dioxan at  $-20^\circ$  the  $\beta$ -lactones failed to react.<sup>32</sup>

*c. Carbon Disulfide.* Reaction of **8** with carbon disulfide and sodium hydride in dimethylformamide at room temperature gave only unchanged **8** and not 1-isoquinolyl phenyl ketone as might have been expected if **20** did not react with carbon disulfide. Addition of methyl iodide shortly after the start of the reaction permitted the isolation of **42**.<sup>27</sup>

<sup>44</sup> L. R. Walters, E. G. Podrebarac, and W. E. McEwen, *J. Org. Chem.* **26**, 1161 (1961).



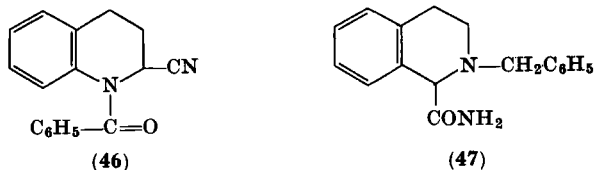
Use of **7** in the above reaction sequence did not lead to a product analogous to **42** but rather to **43**, providing a second example of the reaction of **19** in the 4-position.<sup>27</sup> The formation of **43** can be rationalized by the removal of a proton from intermediate **44** followed by reaction with methyl iodide.



*d. Epoxides.* Several attempts were made to react Reissert anions with epoxides but only in the case of the reaction between **20** and ethylene oxide was there any evidence for the formation of a new product.<sup>33</sup> In this case a compound presumed to be **45** was obtained.

### C. REDUCTIONS

As previously noted<sup>1</sup> the low-pressure reduction of 1-benzoyl-1,2-dihydroquinaldonitrile (**7**) led to the tetrahydro compound (**46**). The purity of **46** has been improved and an alternative synthesis from methyl quinaldate reported.<sup>45</sup>



Reduction of the acid adduct (**12**) of **8** either by catalytic hydrogenation or with sodium borohydride afforded 2-benzyl-1,2,3,4-tetrahydroisoquinaldamide (**47**).<sup>19</sup>

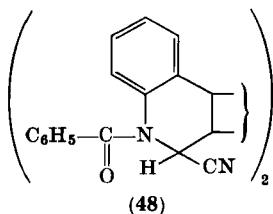
<sup>45</sup> R. F. Collins, *J. Am. Chem. Soc.* **77**, 4921 (1955).



## D. HOMOLYSIS

Photolysis of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**8**) with 2537 Å light in acetonitrile or *tert*-butanol produced 1-cyanoisoquinoline in 50% yield.<sup>46</sup> In benzene solution, using a high-pressure mercury source, the yield of nitrile was lower. The photolyses also produced a low yield of the aldehydic fragment corresponding to the aroyl group.

Photolysis of the quinoline Reissert compound (**7**) showed a marked dependence on the wavelength of the ultraviolet source. With 2537 Å light in acetonitrile an 8% yield of 2-cyanoquinoline and a trace of



benzaldehyde were obtained, while with a high-pressure source and benzene as a solvent a 41% yield of the dimer (**48**) was obtained as the only identifiable photoproduct.<sup>46</sup>

Treatment of the isoquinoline Reissert compound **8** or **2** (R = 3,4,5-(OCH<sub>3</sub>)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>) with benzoyl peroxide in boiling benzene gave 1-cyanoisoquinoline.<sup>46</sup> In contrast **7** was essentially unchanged under these conditions.

## IV. Spectral Properties

The ultraviolet absorption spectra have been reported for a number of Reissert compounds<sup>47, 48</sup> and comparison of these with other systems<sup>48</sup> supports the assigned structure.<sup>1</sup>

The absence of absorption due to a cyano group in the infrared spectra of Reissert compounds was discussed earlier<sup>1</sup> and it is sufficient to note that all of the new Reissert compounds prepared lack absorption in the range 2200–2400 cm<sup>-1</sup>.

<sup>46</sup> P. T. Izzo and A. S. Kende, *Tetrahedron Letters*, 5731 (1966).

<sup>47</sup> I. W. Elliott, Jr. and R. B. McGriff, *J. Org. Chem.* **22**, 514 (1957).

<sup>48</sup> R. F. Collins and T. Henshall, *J. Am. Chem. Soc.* **80**, 159 (1958).

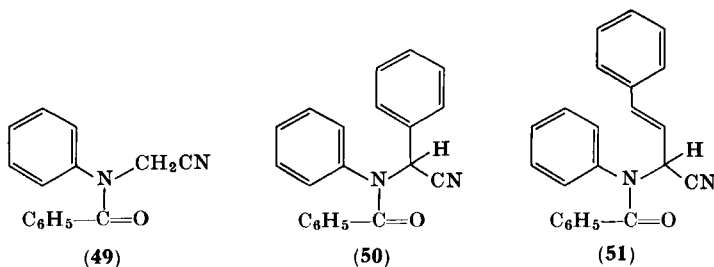
The proton magnetic resonance spectrum of 1-cyano-1,2-dihydro-isoquinaldonitrile (**8**) has been reported<sup>49</sup> and is consistent with the assigned structure. A report on the long-range proton coupling in Reissert compounds has appeared.<sup>49a</sup>

## V. Related Compounds and Reactions

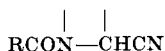
In many cases compounds analogous to Reissert compounds have been reported. No attempt will be made to describe all such reactions in this review, but rather the coverage will be restricted to those in which some direct comparison to **1** and **2** has been or can be made.

### A. REDUCED AND OPEN-CHAIN ANALOGS

Several open-chain analogs of Reissert compounds have been prepared as part of the study of the mechanism of the acid-catalyzed hydrolysis of Reissert compounds. *N*-Benzoyl-*N*-phenylglycinonitrile (**49**) has been prepared from glycolonitrile.<sup>5</sup> Although the infrared and



ultraviolet spectra of **49** are very similar to that of a Reissert compound (**7**), it gives only benzoic acid and no benzaldehyde on acid hydrolysis. The compounds **50** and **51** have been prepared<sup>50</sup> and shown to yield no significant quantities of benzaldehyde on acid hydrolysis. These results indicate that the



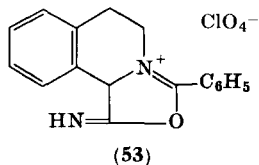
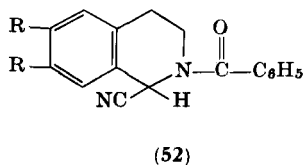
system must be part of a ring for complete analogy to **1** and **2**.

<sup>49</sup> R. Bramley and M. D. Johnson, *J. Chem. Soc.*, 1372 (1965).

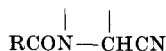
<sup>49a</sup> S. R. Chhabra, J. R. Kershaw, and B. C. Uff, *Tetrahedron Letters*, 3199 (1967).

<sup>50</sup> R. F. Collins and T. Henshall, *J. Chem. Soc.*, 1881 (1956).

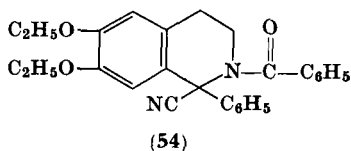
As noted in Section III, C, a pure sample of **46** has now been obtained and this does not give benzaldehyde on acid hydrolysis.<sup>45</sup> Other dihydro Reissert compounds (**52**, R = H and R = OCH<sub>3</sub>) have been prepared by reaction of the appropriate 3,4-dihydroisoquinoline with



benzoyl chloride and potassium cyanide.<sup>19, 34</sup> These do not yield benzaldehyde on acid hydrolysis. Similarly the salt (**53**) obtained from **52** gave only benzoic acid and no benzaldehyde.<sup>19</sup> It therefore seems apparent that not only must the



system be part of a ring but the 3,4 double bond in the ring is also a requirement for behavior as a Reissert compound.



The reaction of 1-phenyl-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline with benzoyl cyanide in benzene-acetic acid gave rise to **54** which on basic hydrolysis yielded 1-phenyl-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide.<sup>51</sup>

## B. ANALOGS WITH GROUPS OTHER THAN CYANO

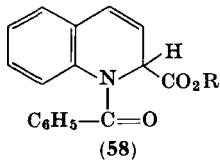
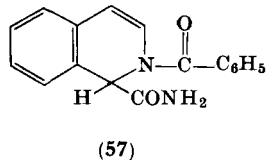
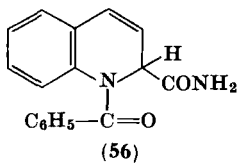
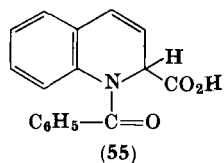
A number of compounds related to **1** and **2** but with groups other than cyano have been reported. These include **55**,<sup>52</sup> **56**,<sup>17</sup> **57**,<sup>53</sup> and **58**.<sup>54</sup> The amides **56** and **57** were prepared by action of hydrogen

<sup>51</sup> J. Gardent, *Compt. Rend.* **247**, 2153 (1958).

<sup>52</sup> R. F. Collins, *Chem. & Ind. (London)*, 736 (1957).

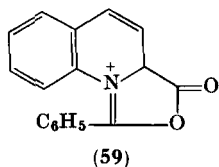
<sup>53</sup> L. R. Walters, *J. Chem. Eng. Data* **9**, 248 (1964).

<sup>54</sup> L. R. Walters, *J. Chem. Eng. Data* **10**, 79 (1965).



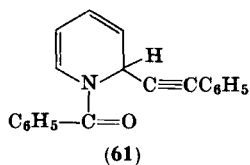
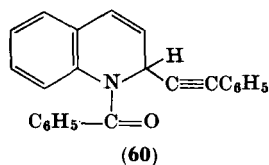
peroxide on the appropriate Reissert compound.<sup>17, 53</sup> The acid **55** was obtained from **56** by selective hydrolysis on an ion exchange resin<sup>52</sup> and the esters **58** were prepared from **55**.<sup>54</sup>

Acid hydrolysis of compounds **55** and **56** by the usual method does not lead to the isolation of any benzaldehyde.<sup>17, 48</sup> It has been shown,



however, that **55** and **56** yield benzaldehyde on hydrolysis provided that they are first treated with a dehydrating agent such as polyphosphoric acid.<sup>48</sup> It has been postulated that the initial dehydration converts **55** to **59**, an intermediate analogous to that (**12**) proposed for the hydrolysis of normal Reissert compounds. The hydrolysis of **59** then would follow the same path as reported for the hydrolysis of **12**.<sup>1</sup>

The reaction of quinoline, benzoyl chloride, and silver phenylacetylide led to the formation of **60**<sup>55</sup> which could be considered as



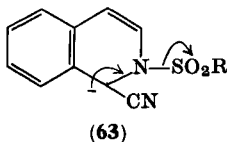
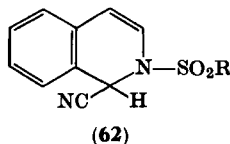
<sup>55</sup> T. Agawa and S. I. Miller, *J. Am. Chem. Soc.* **83**, 449 (1961).

being related to Reissert compound **1**. This same type of compound (**61**) has also been prepared in the pyridine series.<sup>55</sup> This latter observation is of interest since as noted earlier a Reissert compound has yet to be reported in the pyridine series. Acid-catalyzed hydrolysis of **61** is reported<sup>55</sup> to yield benzaldehyde in keeping with its analogy to a Reissert compound. Other reactions of **61**, including hydrolysis in base to 2-stilbazole, have been reported.<sup>55</sup> Preliminary attempts<sup>56</sup> to alkylate compounds of this type in the presence of phenyllithium or sodium hydride have met with little success.

### C. ANALOGS WITH GROUPS OTHER THAN ACYL

#### 1. *N*-Arylsulfonyl and *N*-Alkylsulfonyl Compounds

Isoquinoline, potassium cyanide, and an alkyl- or arylsulfonyl chloride reacted to yield 2-arylsulfonyl- or 2-alkylsulfonyl-1,2-dihydroisoquinolonditriles (**62**).<sup>43</sup> As is the case with Reissert compounds these analogs do not exhibit any nitrile absorption in the



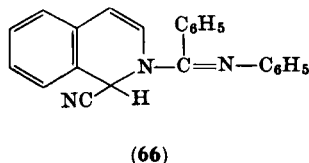
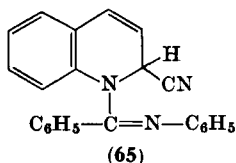
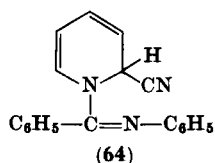
infrared. The chemical behavior of **62** ( $R = C_6H_5$ ) differs from that of the Reissert compound **8**. Treatment of **62** with a base such as sodium hydride, phenyllithium, or 5% sodium hydroxide led to the isolation, in high yield, of isoquinolonditrile.<sup>43, 57</sup> Sodium benzenesulfinate has also been isolated from the sodium hydride reaction. The presence of methyl iodide or benzaldehyde does not alter these results. The fact that  $RSO_2-$  is such a good leaving group undoubtedly accounts for the rapid elimination in **63** rather than alkylation. Under the conditions normally used for acid hydrolysis of Reissert compounds, **62** ( $R = C_6H_5$ ) is hydrolyzed to isoquinoline.<sup>43</sup>

Attempts to prepare quinoline or phthalazine analogs of **62** led only to the isolation of quinaldonitrile<sup>43</sup> and 1-cyanophthalazine,<sup>58</sup> respectively. Undoubtedly this proceeds through the quinoline and phthalazine analogs of **62**.

<sup>56</sup> H. W. Gibson, J. M. Wefer, and F. D. Popp, unpublished results (1965–1966).

<sup>57</sup> J. M. Wefer, A. Catala, and F. D. Popp, *Chem. & Ind. (London)*, 140 (1965).

<sup>58</sup> F. D. Popp, unpublished results (1967).

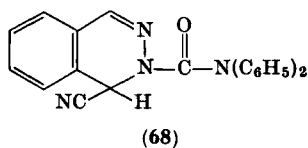
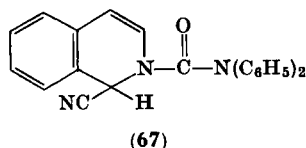


## 2. *N*-Phenylbenzimidyl Compounds

The hydrochlorides of **64**, **65**, and **66** were obtained by reaction of *N*-phenylbenzimidyl chloride and hydrogen cyanide with the appropriate heterocyclic base.<sup>59</sup> As is typical of the Reissert compounds, these three compounds lack absorption peaks in the region 2200–2400  $\text{cm}^{-1}$ . To further the analogy to Reissert compounds, acid-catalyzed hydrolysis of **64**, **65**, and **66** gave benzaldehyde. Picolinic acid, quinaldic acid, and isoquinaldic acid, respectively, as well as aniline, are also obtained from the hydrolysis. Nitrobenzene oxidation of the three compounds gave pyridine-2-carboxamide, quinaldonitrile, and isoquinaldonitrile, respectively.<sup>59</sup>

## 3. *N*-(*N,N*-Diphenylcarbamoyl) Compounds

Reaction of isoquinoline, potassium cyanide, and *N,N*-diphenylcarbamoyl chloride gave **67**.<sup>60</sup> A similar compound was also obtained through the use of *N,N*-diethylcarbamoyl chloride. Again the infrared



was similar to that expected for an analog of **2**. The compound was, however, inert to treatment with both acids and bases using conditions under which both **2** and **62** reacted. Quinoline failed to give an analog of **67**<sup>60</sup> but phthalazine gave **68**.<sup>58</sup>

## 4. *N*-(Carboalkoxy) Compounds

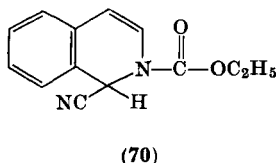
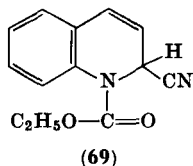
Reaction of quinoline or isoquinoline with potassium cyanide and ethyl chloroformate gave rise to **69** and **70**, respectively.<sup>61</sup> Use of

<sup>59</sup> P. Davis and W. E. McEwen, *J. Org. Chem.* **26**, 815 (1961).

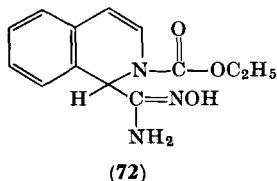
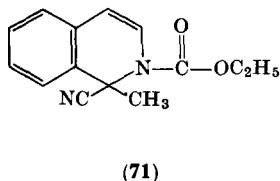
<sup>60</sup> F. D. Popp, J. M. Wefer, and A. Catala, *J. Heterocyclic Chem.* **2**, 317 (1965).

<sup>61</sup> J. M. Wefer and F. D. Popp, unpublished results (1966–1967).

isoquinoline and potassium cyanide with benzyl chloroformate<sup>61</sup> or potassium cyanide and ethyl chloroformate with 5,6-benzoquinoline<sup>62</sup> gave analogous compounds.



Treatment of **70** with sodium hydride and methyl iodide in dimethylformamide gave, in analogy with **2**, compound **71** which was hydrolyzed to isoquinaldine.<sup>61</sup> Reaction of the anion of **70** with benzaldehyde gave an intermediate which could be hydrolyzed to



1-isoquinolyl phenyl carbinol.<sup>61</sup> Reaction of **70** with hydroxylamine gave **72**<sup>62</sup> in analogy with the reaction of **7**.<sup>1</sup>

### 5. Miscellaneous Analogs

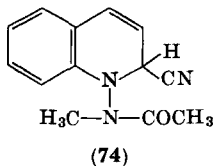
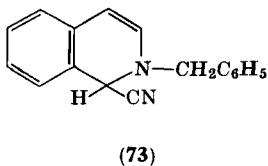
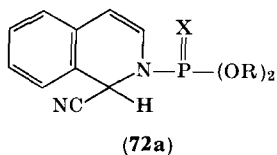
Reaction of isoquinoline and potassium cyanide with dialkyl chlorothiophosphates<sup>62a, 62b</sup> and dialkyl chlorophosphates<sup>62b</sup> gives rise to compounds of the type **72a** (X = S or O).

Treatment of the *N*-benzyl isoquinolinium bromide with potassium cyanide gave **73**.<sup>34</sup> A similar compound was obtained from the ethiodide. Use of potassium thiocyanate in place of potassium cyanide also gave a similar compound. Treatment of **73** or the other analogs with ethanolic picric acid resulted in the liberation of the cyano or thiocyno group to give 2-benzyl- or 2-ethylisoquinolinium picrate.<sup>34</sup> These compounds fail to react as typical Reissert compounds in the presence of phenyllithium or sodium hydride.

<sup>62</sup> L. Katz and F. D. Popp, unpublished results (1966–1967).

<sup>62a</sup> R. W. Young and E. Gelblum, U.S. Patent 3,249,614 (1966).

<sup>62b</sup> D. Spatz and F. D. Popp, unpublished results (1967).



The compound **74** has been proposed as an intermediate in the conversion of *N*-methylacetamidoquinolinium iodide to 2- and 4-cyanoquinoline.<sup>63</sup>

The "Reissert reaction" with quinoline-1-oxide which was noted in the previous review<sup>1</sup> has now been extended to a number of additional heterocyclic *N*-oxides but is considered to be beyond the scope of this review.

<sup>63</sup> T. Okamoto, M. Hirobe, and T. Yamazaki, *Chem. & Pharm. Bull. (Tokyo)* **14**, 512 (1966).



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# Monoazaindoles: The Pyrrolopyridines

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## I. Introduction

In 1885, Fischer and Täuber<sup>1</sup> reported that a sublimate formed during the decomposition of harminic acid, an oxidation product of the alkaloid harmine. They later named it "apoharmine" and prepared several derivatives.<sup>2</sup> This first azaindole was not recognized as such until Perkin and Robinson<sup>3</sup> assigned it a "pyrindole" structure.

<sup>1</sup> O. Fischer and E. Täuber, *Chem. Ber.* **18**, 400 (1885).

<sup>2</sup> O. Fischer, *Chem. Ber.* **22**, 637 (1889).

<sup>3</sup> W. H. Perkin, Jr. and R. Robinson, *J. Chem. Soc.* **101**, 1775 (1912).

Although this group of workers later established the correct structure of apoharmine (**1**,  $R = CH_3$ )<sup>4</sup> its direct synthesis was not reported until 1955.<sup>5</sup>

The only member of this series known to occur in the free state is 7-azaindole (**2**), which was isolated from coal tar by Kruber<sup>6</sup> in 1943. This served as a commercial source for it for some time.

The discovery of serotonin and the development of amino acid analogs as antimetabolites initiated the current interest in azaindoles during the last decade. In addition to providing interesting azalogs of tryptamine and tryptophan, azaindoles have stimulated much research owing to their synthetic elusiveness and variety of properties.

An attempt is made in this review to discuss the practical utility of the various synthetic approaches to azaindoles and to organize their properties. The only benzo derivatives to be considered are a few pyrroloquinolines. The pyridoindoles, or carbolines, have been extensively reviewed.<sup>7</sup> A brief review on the synthesis of azaindoles has been published.<sup>8</sup>

## II. Nomenclature

Perkin and Robinson<sup>3</sup> introduced "pyrindole" as the first nomenclature for the fused pyrrole-pyridine system, numbering the ring as in structure **1**. These workers originally proposed the structure 2-methyl-8-pyrindole for apoharmine,<sup>3</sup> but later showed it to be 8-methyl-7-pyrindole (**1**,  $R = CH_3$ ), i.e., 7-methyl-6-azaindole.<sup>4</sup> They also suggested that the parent ring system, 6-azaindole, be called "harmyrene."<sup>9</sup>

The pyrindole nomenclature persisted until Kruber<sup>6</sup> introduced the aza designation for 7-azaindole (**2**). This is the system which has been used most frequently.

*The Ring Index*<sup>10</sup> and *Chemical Abstracts* classify the system as pyrrolopyridine, numbered as in **2**. Accordingly, 4-azaindole (**3**) is

<sup>4</sup> W. H. Perkin, Jr. and R. Robinson, *J. Chem. Soc.* **115**, 933 (1919).

<sup>5</sup> W. Herz and S. Tocker, *J. Am. Chem. Soc.* **77**, 6355 (1955).

<sup>6</sup> O. Kruber, *Chem. Ber.* **76**, 128 (1943).

<sup>7</sup> R. A. Abramovitch and I. D. Spenser, *Advan. Heterocyclic Chem.* **3**, 79 (1964).

<sup>8</sup> S. Siddappa, *J. Karnatak Univ.* **7**, 26 (1962); cf. F. Möller, in 'Methoden der organischen Chemie' (J. Houben and T. Weyl, eds.), Vol. II, Part I, p. 9. Thieme, Stuttgart, 1957.

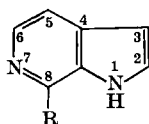
<sup>9</sup> W. Lawson, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **125**, 626 (1924).

<sup>10</sup> A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd ed., p. 166. Am. Chem. Soc., Washington, D.C., 1960.

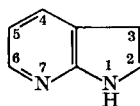
1*H*-pyrrolo[3,2-*b*]pyridine, 5-azaindole (4) is 1*H*-pyrrolo[3,2-*c*]pyridine, 6-azaindole (1, R = H) is 1*H*-pyrrolo[2,3-*c*]pyridine, and 7-azaindole (2) is 1*H*-pyrrolo[2,3-*b*]pyridine. Although this convention has been used in *Chemical Abstracts* since 1925 occasional inconsistencies have appeared in the literature.<sup>10a</sup>

The editors of the *Journal of the Chemical Society* prefer to use the diazaindene nomenclature, according to which compound 2 is 1,7-diazaindene, etc.

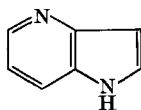
In the present review the azaindole nomenclature is used. In addition to being the most widely adopted and more concise, it lends to a more convenient method of naming azalogs of known compounds, such as 7-azatryptophan.



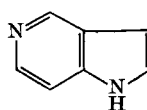
(1)



(2)



(3)



(4)

### III. Synthesis

#### A. VIA THE MADELUNG SYNTHESIS

The most successful method for preparing azaindoles has been the Madelung synthesis,<sup>11</sup> which involves a base-catalyzed cyclization of *o*-acylaminotoluenes or picolines.<sup>12</sup> Eighteen azaindoles have been prepared by various modifications of the Madelung ring closure. These are summarized in Table I.

<sup>10a</sup> Confusion in the earlier period was aided by the use of the name "pyrindol" by A. Angeli [*Gazz. Chim. Ital.* **20**, 761 (1890)], and its adoption by M. Scholtz and W. Fraude [*Chem. Ber.* **46**, 1069 (1913)], for pyrrocoline (indolizine). Scholtz [*Arch. Pharm.* **251**, 666 (1913)] later reported the synthesis of "5- and 7-methyl-pyrindol," which was titled as "pyridine-pyrrole" compounds by *Chem. Abstr.* [**8**, 2698 (1914)]. The situation was resolved by A. E. Tschitschibabin [*Chem. Ber.* **60**, 1607 (1927)] who suggested that the name "indolizine" be adopted for these pyrrolo-[1,2-*a*]pyridines and "pyrindol" be reserved for the azaindoles.

<sup>11</sup> W. Madelung, *Chem. Ber.* **45**, 1128 (1912).

<sup>12</sup> P. L. Julian, E. W. Meyer, and H. C. Printy, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 3, p. 16. Wiley, New York, 1952.

TABLE I  
AZAINDOLES OBTAINED VIA THE MADELUNG SYNTHESIS

Azaindole	Substituent	Yield (%)	Reference
4	—	20,—,10 <sup>a</sup>	13, 14, 15
4	2-Me	ca. 90	13
4	5-Me	12,—	16, 16a
4	2,5-Dimethyl	55	16
4	2-Ph, 5-Me	67,71	16, 17
5	—	51 <sup>a</sup> ,21	15, 18
5	2-Me	1	13
6	2-Me	23,30–40	19, 20
6	2-Ph	24	20a
6	2-(2-pyridyl)	32	20a
6	2-(4-pyridyl)	12	20a
7	—	—,57,80 <sup>a</sup> ,3,52	14, 15, 15, 21, 22
7	2-Me	17	21
7	2-Et	12	21
7	3-Me	16	22
7	4-Me	24	23
7	5-Me	38,35 <sup>a</sup>	23, 24
7	6-Me	13	23

<sup>a</sup> Yield indicated is for cyclization of preformed amidine.

Koenigs and Fulde<sup>19</sup> were the first to synthesize an azaindole directly by heating 3-acetamido-4-picoline (5, R=Me) with sodium

<sup>13</sup> G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 198 (1948).

<sup>14</sup> T. K. Adler and A. Albert, *J. Chem. Soc.*, 1794 (1960).

<sup>15</sup> R. R. Lorenz, B. F. Tullar, C. F. Koelsch, and S. Archer, *J. Org. Chem.* **30**, 2531 (1965).

<sup>16</sup> J. C. Clayton and J. Kenyon, *J. Chem. Soc.*, 2952 (1950).

<sup>16a</sup> Sterling Drug Inc., Netherlands Patent 6,414,916 (1965); *Chem. Abstr.* **64**, 8152 (1966).

<sup>17</sup> M. Protiva, J. O. Jílek, Z. J. Vejdělek, and O. Exner, *Chem. Listy* **46**, 551 (1952); *Chem. Abstr.* **48**, 2710 (1954).

<sup>18</sup> S. Okuda and M. M. Robison, *J. Org. Chem.* **24**, 1008 (1959).

<sup>19</sup> E. Koenigs and A. Fulde, *Chem. Ber.* **60**, 2106 (1927).

<sup>20</sup> W. Herz and D. R. K. Murty, *J. Org. Chem.* **25**, 2242 (1960).

<sup>20a</sup> M. Hooper, D. A. Patterson, and D. G. Wibberley, *J. Pharm. Pharmacol.* **17**, 734 (1965).

<sup>21</sup> G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 603 (1945).

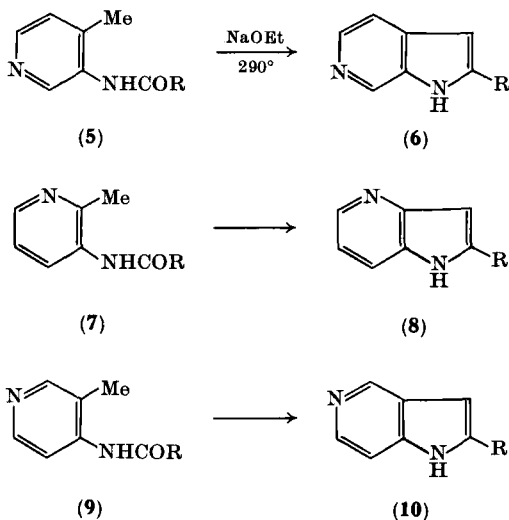
<sup>22</sup> M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.* **77**, 457 (1955).

<sup>23</sup> A. Albert and R. E. Willette, *J. Chem. Soc.*, 4063 (1964).

<sup>24</sup> R. E. Willette, unpublished results (1966).

ethoxide at  $290^{\circ}$  for 10 minutes to give 2-methyl-6-azaindole (6, R = Me) in 23 % yield.

Similarly, Clemo and Swan<sup>21</sup> synthesized 7-azaindole (2) and its 2-methyl and 2-ethyl derivatives in low yields (3, 17, and 12 %, respectively). They failed to improve the yield by use of potassium

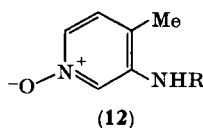
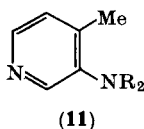


ethoxide, which Tyson<sup>25</sup> reported to give a higher yield of indole. Clemo and Swan<sup>13</sup> later found that cyclization of 3-formamido-2-picoline (7, R = H) did not proceed with sodium ethoxide, whereas use of potassium ethoxide at  $350^{\circ}$  gave 4-azaindole (8, R = H) in 20 % yield. 3-Diacetylamino-2-picoline cyclized in high yield to 2-methyl-4-azaindole (8, R = Me) with sodium ethoxide, and 4-acetamido-3-picoline (9, R = Me) gave 2-methyl-5-azaindole (10, R = Me). Use of potassium *tert*-butoxide<sup>25</sup> did not improve the yields. 5-Azaindole (10, R = H) could not be obtained from 4-formamido-3-picoline (9, R = H) with any of the alkoxides.

Clayton and Kenyon<sup>16</sup> prepared 5-methyl-, 2,5-dimethyl-, and 2-phenyl-5-methyl-4-azaindole in 12, 55, and 67 % yields, respectively, by treatment of the corresponding formyl, acetyl, and benzoyl derivatives of 3-amino-2,6-dimethylpyridine with sodium ethoxide at  $310^{\circ}$  for 15 minutes. The phenyl compound was prepared also by Protiva *et al.*<sup>17</sup> in 71 % yield.

<sup>25</sup> F. T. Tyson, *J. Am. Chem. Soc.* **63**, 2024 (1941).

The first significant improvement in the Madelung approach to azaindoles was introduced by Robison and Robison<sup>22</sup> who obtained 7-azaindole (**2**) in 52% yield by using sodium anilide as the base together with potassium formate, another of Tyson's<sup>26</sup> modifications. More efficient heating gave yields of about 45% on a 0.3 *M* scale.<sup>27</sup> Applying these conditions to the formyl isomer (**9**, R = H) gave 5-azaindole (**10**, R = H) in 21% yield.<sup>18</sup> Herz and Murty<sup>28</sup> were unable to repeat this last cyclization. Also, they<sup>20</sup> recovered 3-amino-4-picoline (**11**, R = H) (25–40%) on treating the formamide (**5**, R = H) with sodium anilide, sodium ethoxide, or the sodium salt of the amine (**11**, R = H). Attempts on the *N*-oxides of the formyl (**12**, R = CHO) and acetyl (**12**, R = Ac) compounds gave similar results. It was hoped that the increased acidity of the methyl hydrogens in the *N*-oxides would facilitate cyclization. Treatment of the formyl *N*-oxide with



lithium amide in dimethylformamide resulted in hydrolysis to the amine (**12**, R = H), whereas the acetyl *N*-oxide gave 2-methyl-6-azaindole (**6**, R = Me) (5%), obtained also from the diacetyl amine (**11**, R = Ac), but in good yields (30–40%). The monoacetyl compound (**5**, R = Me) gave only a 5% yield, in contrast to the higher yield claimed earlier.<sup>19</sup>

The Robison's modification was employed for the synthesis of 4-azaindole,<sup>14</sup> and 4-, 5-, and 6-methyl-7-azaindoles.<sup>23</sup>

2-Phenyl-, 2-(2-pyridyl)-, and 2-(4-pyridyl)-6-azaindoles were synthesized from the corresponding 3-amido-4-picolines with sodium ethoxide at 325°.<sup>20a</sup>

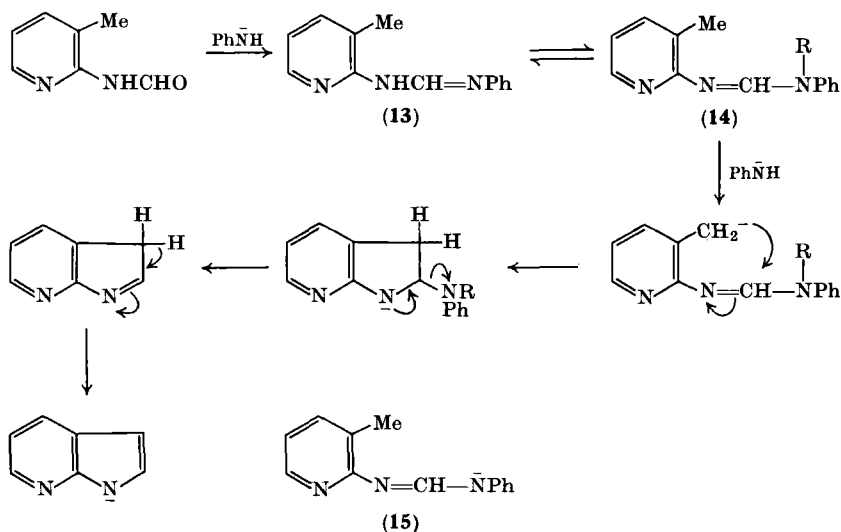
In spite of these reported successes, the Madelung cyclization offers the following disadvantages: (i) the drastic conditions necessary limit its application to the synthesis of unsubstituted or alkyl- and aryl-substituted azaindoles; (ii) the reaction is often, if not always, intractable; and (iii) yields are erratic, often unreproducible, and subject to such variables as stirring and heating<sup>27</sup> efficiency, purity of starting materials,<sup>18</sup> quality (or manufacturer!) of reagents,<sup>27</sup> and operator.

<sup>26</sup> F. T. Tyson, *J. Am. Chem. Soc.* **72**, 2801 (1950).

<sup>27</sup> M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.* **77**, 6554 (1955).

<sup>28</sup> W. Herz and D. R. K. Murty, *J. Org. Chem.* **26**, 122 (1961).

Many of these disadvantages have been eliminated or minimized by the detailed studies of Lorenz *et al.*<sup>15, 16a</sup> Initially, consistent yields (50–63 %) of 7-azaindole were obtained on a 3-mole scale by employing several modifications including the use of mineral oil as a diluent. These workers established the mechanism of the cyclization (Scheme 1) when sodium anilide is used as the base. A yield of 52 % was obtained when the formimide (16) was heated at 200° with sodium *N*-methylanilide, forming amidine 14 R = Me and preventing tautomerization



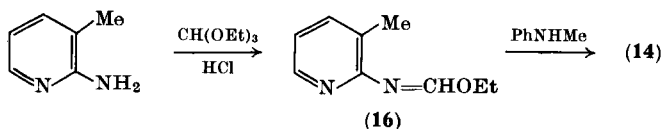
SCHEME 1

to amidine 13 and formation of ion 15. At 300°, normally employed, the yield fell to 38 %. Optimum conditions were obtained by use of the preformed amidine (14, R = Me), prepared by treating 2-amino-3-picoline with ethyl orthoformate, followed by condensation of the resulting formimide (16) with *N*-methylaniline. Amidine 14 (R = Me) cyclized to 7-azaindole in 80 % yield when refluxed (198°) with sodium *N*-methylanilide in *N*-methylaniline (70 % overall yield from the amine). Similarly, 4-amino-3-picoline and 3-amino-2-picoline were converted into the formamidines, which gave 5- and 4-azaindoles in 51 and 10 % yields (36 and 6 % overall), respectively. Attempts to prepare 6-azaindole were not made.<sup>29</sup> Curiously, 300° was required to cyclize the corresponding tolyl compound to indole (76 % yield).

<sup>29</sup> R. R. Lorenz, private communication (1967).

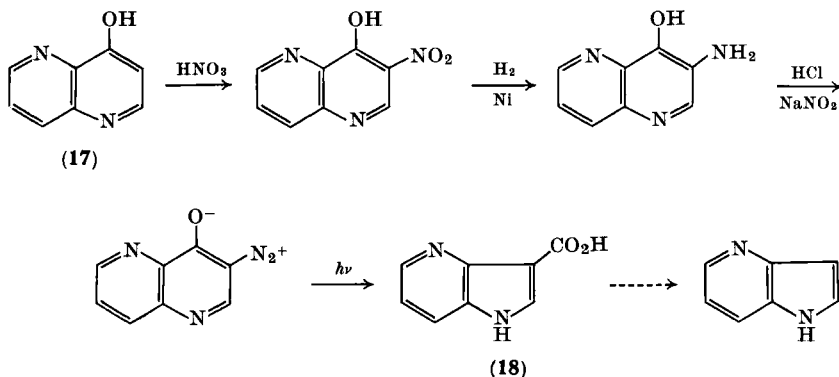


5-Methyl-7-azaindole was prepared in 35 % yield by this sequence.<sup>24</sup> To date it is the best method for the synthesis of 5- and 7-azaindole, and serves as a commercial preparation for the latter.



### B. BY PHOTOCHEMICAL RING CONTRACTION OF NAPHTHYRIDINES

In a series of papers on the photochemical synthesis of cyclopentadiene and pyrrole derivatives, Süss and Möller<sup>30</sup> reported the preparation of indoles which could not be made by the Fischer method. Primarily, these were indoles with electron-withdrawing substituents in the benzene ring. Included was the synthesis of 4-azaindole-3-carboxylic acid (**18**, Scheme 2). The reaction was extended to the synthesis of the other three azaindoles.<sup>31, 32</sup>



SCHEME 2

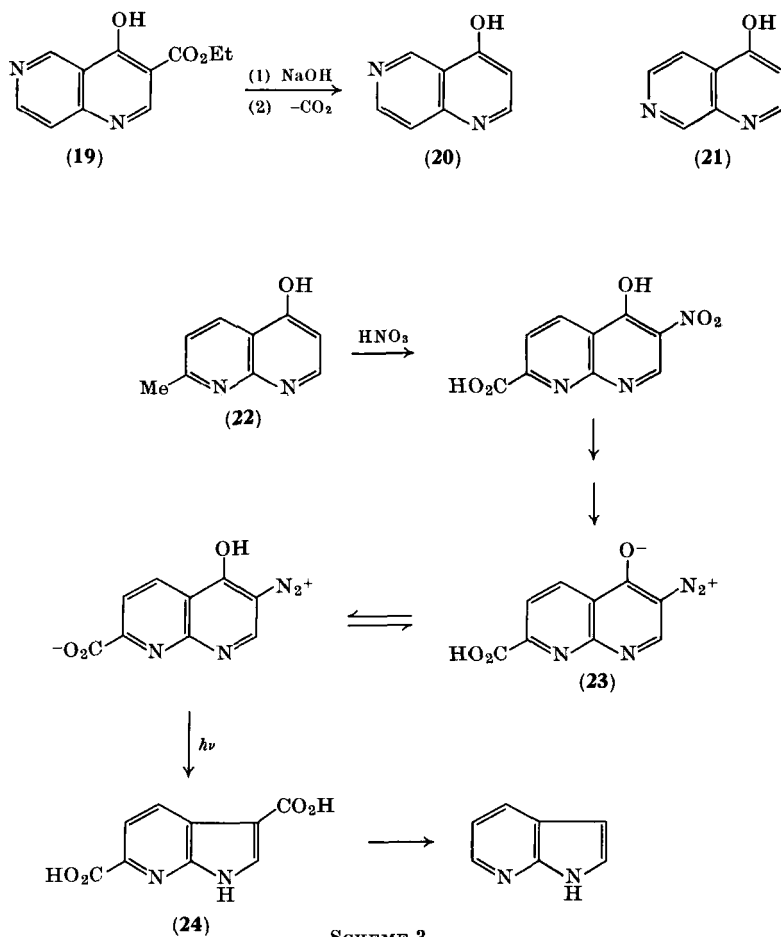
Although the reaction is lengthy and unconventional, which has discouraged its use by some workers,<sup>18, 20</sup> it warrants discussion as a useful synthesis of azaindoles, because it is the only method by which all four parent compounds can be prepared and it is reliable.

<sup>30</sup> O. Süss and K. Möller, *Ann. Chem.* **593**, 91 (1955).

<sup>31</sup> O. Süss and K. Möller, *Ann. Chem.* **599**, 233 (1956).

<sup>32</sup> K. Möller and O. Süss, *Ann. Chem.* **612**, 153 (1958).

The reaction sequence involves refluxing the appropriate 4-hydroxy-naphthyridine in concentrated nitric acid, followed by reduction of the nitro compound over Raney nickel at room temperature and



SCHEME 3

atmospheric pressure. The amine is diazotized with sodium nitrite in *N*-hydrochloric acid at 0°, taking the reaction mixture rapidly to dryness at low temperature. Irradiation of the diazo oxide in dilute acetic acid at 20° with ultraviolet light gives the 3-carboxylic acid<sup>14</sup> (Scheme 2). Yields for each step range from ca. 50 to 90 %.

Süs and Möller<sup>30</sup> reported yields of 46, 57, and 70 %, respectively, for the first three steps starting from the 1,5-naphthyridine (**17**), but did not give a yield for the 4-aza acid (**18**), which was isolated as the hydrochloride. They state that attempts to decarboxylate this salt [*sic*] met with difficulty, and work was continuing. Unfortunately, the following papers<sup>31, 32</sup> do not report the decarboxylation. This is surprising, since heating the 6-aza acid to its melting point gives 6-azaindole in 96 % yield,<sup>31</sup> and similarly 5-azaindole is obtained in 86 % yield.<sup>32</sup> The 7-aza diacid (**24**, Scheme 3) decarboxylated in 75 % yield.<sup>32</sup>

The required 4-hydroxy-1,6-naphthyridine (**20**) is prepared by condensation of ethoxymethylenemalonic ester (EMME) with 4-aminopyridine, giving the 1,6 ester (**19**), which is readily hydrolyzed with alkali and the acid decarboxylated in refluxing quinoline.<sup>32-34</sup> Similarly, 3-aminopyridine gives the 1,5 isomer (**17**),<sup>35, 36</sup> and 3-aminopyridine 1-oxide gives the 1,7 isomer (**21**).<sup>33, 37</sup> 2-Aminopyridine cyclizes onto the ring nitrogen with EMME, whereas its 6-methyl derivative led to the 7-methyl-1,8 isomer (**22**).<sup>38</sup> As shown in Scheme 3, this methyl group oxidizes during nitration, and the nitro acid formed was reduced with sodium dithionite in 42 % yield. The diacid (**24**) was obtained in 89 % yield from the diazo oxide (**23**).<sup>32</sup>

Obvious disadvantages of the photochemical method, in addition to its lengthiness, are: (i) its unproven adaptability to the preparation of substituted azaindoles; (ii) its dependence upon the availability of suitably substituted aminopyridines; and (iii) the difficulties in its application to molar-scale preparations.

### C. VIA THE FISCHER INDOLE SYNTHESIS

The synthesis of azaindoles by the Fischer indole synthesis has been tried more often than by any other method. It has given varied results, with over thirty successful ring closures of pyridyl- or quinolyl-hydrazones reported. Most of these have led to carboline deriva-

<sup>33</sup> A. Albert, *J. Chem. Soc.*, 1790 (1960).

<sup>34</sup> C. R. Hauser and G. A. Reynolds, *J. Org. Chem.* **15**, 1224 (1950).

<sup>35</sup> C. C. Price and R. M. Roberts, *J. Am. Chem. Soc.* **68**, 1204 (1946).

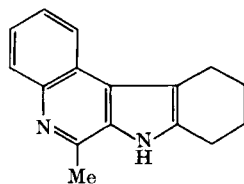
<sup>36</sup> J. T. Adams, C. K. Bradsher, D. S. Breslow, S. T. Amore, and C. R. Hauser, *J. Am. Chem. Soc.* **68**, 1317 (1946).

<sup>37</sup> J. C. Murray and C. R. Hauser, *J. Org. Chem.* **19**, 2008 (1954).

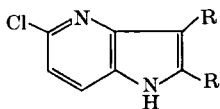
<sup>38</sup> G. R. Lappin, *J. Am. Chem. Soc.* **70**, 3348 (1948).

tives<sup>39-47</sup> or pyrroloquinolines.<sup>43</sup> Only nine substituted azaindoles<sup>41, 45, 46, 48, 49, 49a</sup> and four azaindolenines<sup>46, 50, 51</sup> have been prepared by the Fischer cyclization. Abramovitch and Saha<sup>52</sup> discuss some of these reactions, pointing out the necessity of more vigorous conditions than are necessary to effect ring closure onto a benzene ring.

Early attempts to cyclize 2-quinolyldiazones of acetone,<sup>53</sup> acetaldehyde, acetophenone, and pyruvic acid, and a number of 2-pyridyldiazones,<sup>54</sup> under a variety of conditions failed. Later, however, Robinson and Robinson<sup>39</sup> found that heating 2-methyl-3-hydrazinoquinoline in cyclohexanone gave only a product of uncertain structure described as a dioxide of the hydrazone, but in the presence



(25)



(26)

- <sup>39</sup> G. M. Robinson and R. Robinson, *J. Chem. Soc.* **125**, 827 (1924).  
<sup>40</sup> G. R. Clemo and R. J. W. Holt, *J. Chem. Soc.*, 1313 (1953).  
<sup>41</sup> S. Okuda and M. M. Robison, *J. Am. Chem. Soc.* **81**, 740 (1959).  
<sup>42</sup> F. G. Mann, A. F. Prior, and T. J. Willcox, *J. Chem. Soc.*, 3830 (1959).  
<sup>43</sup> T. R. Govindachari, S. Rajappa, and V. Sudarsanam, *Tetrahedron* **16**, 1 (1961).  
<sup>44</sup> R. A. Abramovitch and K. A. H. Adams, *Can. J. Chem.* **40**, 864 (1962).  
<sup>45</sup> A. H. Kelly, D. H. McLeod, and J. Parrick, *Can. J. Chem.* **43**, 296 (1965).  
<sup>46</sup> A. H. Kelly and J. Parrick, *Can. J. Chem.* **44**, 2455 (1966).  
<sup>47</sup> L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, *Dokl. Akad. Nauk SSSR* **169**, 361 (1966); *Proc. Acad. Sci. USSR, Chem. Sect. (English Transl.)* **169**, 705 (1966).  
<sup>48</sup> Deutsche Gold- und Silber-Scheideanstalt vorm. Roessler, British Patent 259,982 (1925); *Chem. Zentr.* **99I**, 2311 (1928). Curiously, this patent does not appear to have been abstracted by *Chem. Abstr.* However, all the compounds, except the azaindoles, did appear in French Patent 641,422 (1926); *Chem. Abstr.* **23**, 1139 (1929).  
<sup>49</sup> T. Takahashi, H. Saikachi, H. Goto, and S. Shimamura, *J. Pharm. Soc. Japan* **64**, 7 (1944); *Chem. Abstr.* **45**, 8529 (1951).  
<sup>49a</sup> P. A. Crooks and B. Robinson, *Chem. & Ind. (London)*, 547 (1967).  
<sup>50</sup> G. E. Ficken and J. D. Kendall, *J. Chem. Soc.*, 3202 (1959).  
<sup>51</sup> G. E. Ficken and J. D. Kendall, *J. Chem. Soc.*, 584 (1961).  
<sup>52</sup> R. A. Abramovitch and J. G. Saha, *Advan. Heterocyclic Chem.* **6**, 333 (1966).  
<sup>53</sup> W. H. Perkin, Jr. and R. Robinson, *J. Chem. Soc.* **103**, 1973 (1913).  
<sup>54</sup> R. G. Fargher and R. Furness, *J. Chem. Soc.* **107**, 688 (1915).

of a small amount of acetic acid it led directly to the benzocarboline (25) in 63% yield. Interestingly, this procedure has not reportedly been tried on any pyridylhydrazine.

It was claimed that the cyclization of the 2-chloro-5-pyridylhydrazones of acetone and propionaldehyde with zinc chloride at 200° gave 5-chloro-2-methyl-4-azaindole (26, R = H, R' = Me; m.p., 209–210°) and 5-chloro-3-methyl-4-azaindole (26, R = Me, R' = H; m.p., 199–202°), respectively.<sup>48</sup> This patent also claims the synthesis of the same hydrazones of 2-hydrazino-5-nitropyridine, without reporting any cyclization attempts, and its ethyl acetoacetate hydrazone, which cyclized at 120° to give a 1-pyridyl-3-methylpyrazolin-5-one. Pieroni<sup>55</sup> describes the formation of a similar compound by heating ethyl acetoacetate 2-chloro-5-pyridylhydrazone (m.p., 143°; the patent<sup>48</sup> reporting the same hydrazone with m.p. 123–124°) in acetic acid at 100°. More recently, Takahashi *et al.*<sup>49</sup> reported the synthesis of the 2-methyl-4-azaindole (26, R = H, R' = Me) by the same procedure described in the earlier patent (although not referring to it), but their product had m.p. 167°. The 4 (and not the 6) isomer has been assumed in all three cases. Much of this work needs to be confirmed.<sup>56</sup>

Räth<sup>57</sup> synthesized 3-hydrazinopyridine and prepared its propionaldehyde and pyruvic acid hydrazones with the intention of using them to make "pyrindoles" (azaindoles). Although he indicated the work was to be described in a subsequent publication, no mention of it could be found.

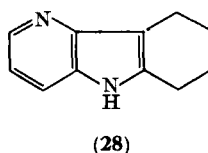
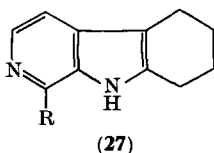
Efforts to synthesize apoharmine (1, R = Me) by Fischer cyclization of ethyl pyruvate 2-methyl-3-pyridylhydrazone failed, whereas its cyclohexanone hydrazone gave tetrahydroharman (27, R = Me) in 11% yield on heating with zinc chloride.<sup>40</sup> This yield seems quite low compared to the 94% yield of a 2:1 mixture of tetrahydro- $\delta$ -carboline (28) and tetrahydro- $\beta$ -carboline (27, R = H), respectively, obtained from cyclohexanone 3-pyridylhydrazone under similar conditions.<sup>44</sup>

Okuda and Robison<sup>41</sup> were able to cyclize cyclohexanone 2-pyridylhydrazone to 5,6,7,8-tetrahydro- $\alpha$ -carboline in 53% yield on heating in polyphosphoric acid, but the acetaldehyde, acetone, and pyruvic acid

<sup>55</sup> A. Pieroni, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fiz. Mat. Nat.* [6] 5, 303 (1927); *Chem. Abstr.* 21, 1814 (1927).

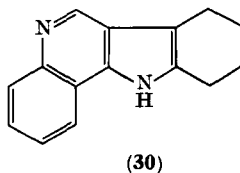
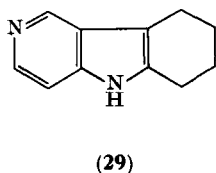
<sup>56</sup> As a start, acetone 2-chloro-5-pyridylhydrazone (m.p. 171–172°) was prepared, but was recovered unchanged after heating with polyphosphoric acid at 200°.

<sup>57</sup> C. Räth, *Ann. Chem.* 486, 95 (1931).

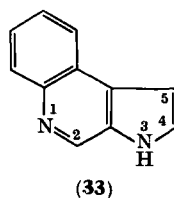
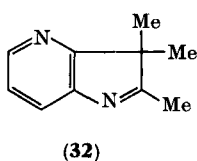
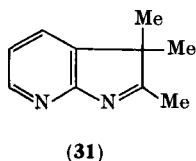


hydrazones failed to react. However, the desoxybenzoin hydrazone gave 2,3-diphenyl-7-azaindole in 12% yield.<sup>41</sup> Cyclohexanone 4-pyridyl- and 4-quinolylhydrazones also cyclized on heating with zinc chloride at 240° to give the  $\gamma$ -carboline (29) (48% yield as  $\text{H}_2\text{ZnCl}_4$  salt) and benzo derivative (30), respectively.<sup>42</sup> The corresponding *N*-methyl- and *N*-phenyl-quinol-4-one hydrazones failed to cyclize under a variety of conditions, including polyphosphoric acid, zinc chloride, and boron trifluoride.

Some success at preparing azaindolenines (3*H*-pyrrolopyridines) by Fischer cyclization was obtained by Ficken and Kendall.<sup>50, 51</sup>



Isopropyl methyl ketone 2-pyridylhydrazone and 3-pyridylhydrazone on heating with zinc chloride gave 2,3,3-trimethyl-7-azaindolenine (31)<sup>50</sup> and 2,3,3-trimethyl-4-azaindolenine (32)<sup>51</sup> in 29 and 23% yields, respectively. They established the latter structure on the basis of infrared spectra, and did not report the isolation of any of the 6 isomer. The 5 isomer was reported as unpublished work, presumably prepared in a similar manner.<sup>51</sup>



Govindachari *et al.*<sup>43</sup> prepared several 3*H*-pyrrolo[2,3-*c*]quinolines (33) in low yield by heating 3-quinolylhydrazones with a large excess of zinc chloride at 260° or in refluxing *p*-cymene. These included the parent 33, obtained directly from the ethyl pyruvate hydrazone in

15% yield, 4-methyl-, 4,5-dimethyl-, 4-ethyl-5-methyl-, 4-phenyl-, 4-phenyl-5-methyl-, and 4,5-diphenyl derivatives. The  $\alpha$ -tetralone hydrazone gave 12,13-dihydro-7*H*-dibenz[*c,i*]- $\beta$ -carboline.

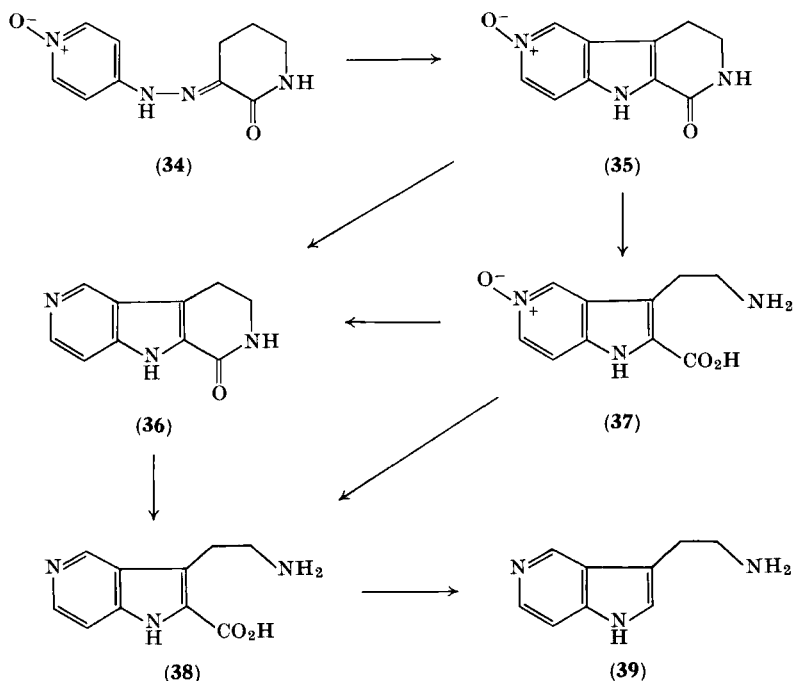
The biologically interesting azalog 5-azatryptamine (39) was synthesized by Pietra and Tacconi<sup>58</sup> by an application of Abramovitch's<sup>59</sup> carboline and tryptamine synthesis involving a Fischer cyclization. Treatment of diazotized 3-aminopyridine 1-oxide with 2-piperidone-3-carboxylic acid at  $-10^\circ$  gave the hydrazone (34) in 72% yield. It was cyclized at  $200^\circ$  in a mixture of zinc and sodium chlorides to give the novel 2,6-diazacarbazole 6-oxide<sup>60</sup> (35) in 32% yield. Hydrolysis with acid or base gave the acid oxide (37) (87%). Attempts to decarboxylate acid 37 in quinoline at  $235^\circ$  led to the deoxygenated carboline (36), which was obtained in 80% yield by hydrogenation of oxide 35 over palladium at room temperature. Similarly, oxide 37 was reduced to the acid amine (38) in 82% yield. Hydrolysis of the amide (36) also gave the acid (38) (86%), which was smoothly decarboxylated with copper in boiling quinoline to 5-azatryptamine (39), isolated in 71% yield as the *N*-acetyl derivative of 39. This is a significant synthesis as 5-azaindole does not react like indole at the 3-position (see Section IV, C,3).

Recent work on the thermal indolization of arylhydrazones has introduced new synthetic possibilities for azaindoles. Kelly *et al.*<sup>45</sup> refluxed cyclohexanone and deoxybenzoin 2-pyridylhydrazones in diethylene glycol to give 5,6,7,8-tetrahydro- $\alpha$ -carboline (42, R=H) and 2,3-diphenyl-7-azaindole in 70 and 56% yields, respectively, compared with 53 and 12% reported earlier.<sup>41</sup> Similarly,  $\gamma$ -carboline 29 was obtained in 95% yield from cyclohexanone 4-pyridylhydrazone (lit. 48%<sup>42</sup>). Several 7-azaindole derivatives were prepared in the same manner.<sup>46</sup> The yields ranged from 5% for azaindolenine (31) to 88% for 3-phenyl-7-azaindole. 3,3-Dimethyl-7-azaindolenine was obtained in 47% yield from the isobutyraldehyde hydrazone. The novel cyclic compounds 40 and 41 were obtained from the 2-pyridylhydrazones of cyclopentanone,  $\alpha$ -indanone, and  $\alpha$ -tetralone in 67, 95, and 77% yields, respectively. Unfortunately, all attempts to cyclize the acetone, pyruvic acid, and ethyl pyruvate hydrazones were unsuccessful. Also, cyclohexanone and methyl ethyl ketone 5-nitro-2-

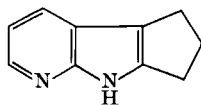
<sup>58</sup> S. Pietra and G. Tacconi, *Farmaco (Pavia)*, *Ed. Sci.* **19**, 741 (1964).

<sup>59</sup> R. A. Abramovitch and D. Shapiro, *J. Chem. Soc.*, 4589 (1956).

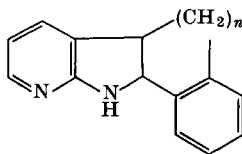
<sup>60</sup> According to the *Ring Index* system, the complete name is 1-oxo-1,2,3,4-tetrahydro-9*H*-pyrrolo[2,3-*c*:4,5-*c'*]dipyridine 6-oxide.



pyridylhydrazones fail to cyclize. Kelly and Parrick<sup>46</sup> explain that protonation of the hydrazino nitrogen may not be essential in the Fischer indole synthesis, but may be necessary when enehydrazine formation is difficult.<sup>61</sup> Under normal Fischer indolization conditions, the pyridine ring is protonated or associated with the metal ion, deactivating it for the electrophilic cyclization stage of the reaction.



(40)

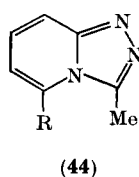
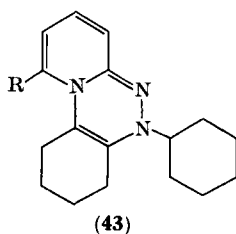
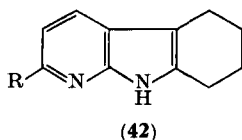
(41,  $n = 1, 2$ )

<sup>61</sup> For a general discussion of the mechanism of this reaction see R. Robinson, *Chem. Rev.* **63**, 372 (1963).



Crooks and Robinson<sup>49a</sup> have used this method to prepare 2,3-dimethyl-5-azaindole in 14.5% yield from isobutyraldehyde 4-pyridylhydrazone, obtaining none of the expected 3,3-dimethyl-5-azaindolenine. The ethyl methyl ketone hydrazone gave the same azaindole in 51.5% yield. These authors also suggest that the 3,3-dimethyl-7-azaindolenine reported by Kelly and Parrick<sup>46</sup> is in fact the rearranged product 2,3-dimethyl-7-azaindole. There is no evidence to date to support either structure.

In all of the Fischer cyclizations of 2-pyridylhydrazones discussed above, only the normal products were reported. Recently, however, Yakhontov *et al.*<sup>47</sup> isolated from the treatment of cyclohexanone 2-pyridylhydrazone with refluxing hydrochloric acid the pyrido-[2,1-*c*]-*as*-triazine (**43**, R = H), in 37% yield, in addition to 20% of the



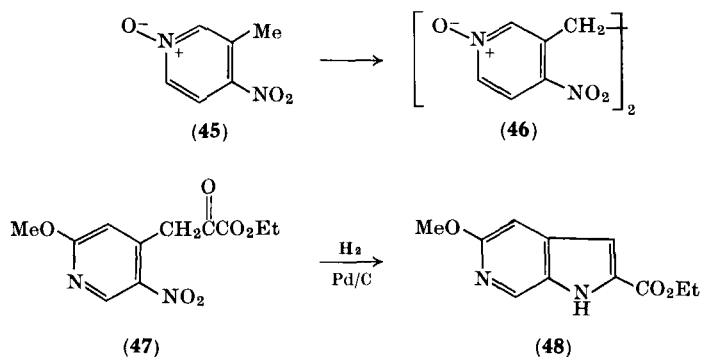
expected  $\alpha$ -carboline (**42**, R = H). The yield of by-product **43** increased to 50% if cyclohexanone was present in the reaction mixture. The 6-methyl hydrazone gave the  $\alpha$ -carboline (**42**, R = Me) (66%) and triazine (**43**, R = Me) (26%). Heating these hydrazones with boron trifluoride-ethyl etherate in acetic acid at 180° in a sealed tube gave the triazolo[4,3-*a*]pyridines (**44**, R = H, Me) in 45 and 67% yields, respectively. Some (28%)  $\alpha$ -carboline (**42**, R = Me) was isolated from the last reaction. The structures of these by-products were established by means of their ultraviolet and mass spectra.<sup>47</sup>

The principal disadvantage of the Fischer indole approach is its failure to provide a route to the parent azaindoles.

#### D. VIA THE REISSERT SYNTHESIS

The Reissert synthesis of indoles has found much success with *o*-nitrotoluenes, but has been tried for the synthesis of azaindoles in only a few cases. Herz and Murty<sup>28</sup> first reported unsuccessful attempts at base-catalyzed condensation of ethyl oxalate with 4-nitro-3-picoline and its *N*-oxide (**45**). No conditions were reported. Later,

Badger and Rao<sup>62</sup> reported that the treatment of the *N*-oxide (45) with potassium ethoxide and ethyl oxalate in ethanol at room temperature gave none of the expected pyruvate but a little of the bispicolyl (46). It had been shown in 1954 that 2- and 4-picoline 1-oxides readily condensed with ethyl oxalate to give the pyruvates in good yield.<sup>63</sup> The electron-attracting influence of the *N*-oxide is known to make the 2- and 4-methyls more acidic, as in the case with the picolines themselves. It was expected that 3-nitro-2- or 3-nitro-4-picolines should give better results. Preliminary trials with these compounds<sup>64</sup> and with 3-nitro-2-picoline 1-oxide<sup>65</sup> failed. Recently, however, Frydman *et al.*<sup>66</sup> reported the successful realization of this reaction. 2-Methoxy-



5-nitro-4-picoline was treated with ethyl oxalate and potassium ethoxide to give the pyruvate (47) in 93 % yield. Hydrogenation with palladium on carbon gave the 6-azaindole-2-carboxylate (48) in 85 % yield. Rapoport<sup>67</sup> states that potassium ethoxide was found to be the most effective catalyst, and that the reaction has been extended to a large number of 4- and 6-azaindoles, with and without the alkoxy group.

<sup>62</sup> G. M. Badger and R. P. Rao, *Australian J. Chem.* **17**, 1399 (1964).

<sup>63</sup> R. Adams and S. Miyano, *J. Am. Chem. Soc.* **76**, 3168 (1954).

<sup>64</sup> A. Albert and G. Johnson, unpublished results (1961).

<sup>65</sup> R. E. Willette, unpublished results (1963); see Willette (ref. 92) for the synthesis of this compound.

<sup>66</sup> B. Frydman, M. E. Despuy, and H. Rapoport, *J. Am. Chem. Soc.* **87**, 3530 (1965).

<sup>67</sup> H. Rapoport, private communication (1966).

General application of the Reissert synthesis does not seem likely, although it may prove to be quite useful for the synthesis of 4- and 6-azaindoles. The nitropicolines are fairly readily available from existing pyridine reactions.

#### E. VIA AZAINDOLINE INTERMEDIATES

Kruber<sup>6</sup> reported that high-pressure hydrogenation of 7-azaindole at 200° gave the 2,3-dihydro compound, 7-azaindoline. This was confirmed by Robison *et al.*<sup>68</sup> (see Section IV,B). Although no yield is given, these workers<sup>69</sup> made use of it to prepare 5- and 6-substituted derivatives of the indoline. Nitration of 7-azaindoline at -5° gave the 1-nitramine in 98% yield. This was rearranged in sulfuric acid to 5-nitro-7-azaindoline (46%), which was reduced to the 5-amine. Dehydrogenation of the 5-nitro compound with palladium on carbon in Dowtherm to 5-nitro-7-azaindole (50%) was then followed by reduction at room temperature to give 5-amino-7-azaindole in 93% yield. 7-Azaindoline 7-oxide, prepared in 46% yield by peracetic acid oxidation of the 1-carbethoxy derivative, was treated with acetic anhydride at room temperature to give a mixture of 1-acetyl-5- and 1-acetyl-6-acetoxy-7-azaindoline (21 and 31%, respectively). They were separated by acid extraction of an ether solution, the weakly basic 6-acetoxy isomer remaining in the ether. The hydroxy indolines were obtained by hydrolysis, the 6 isomer exhibiting a characteristic pyridone absorption in its ultraviolet and infrared spectra (see Sections V,B,1 and 2). The diacetyl derivatives were dehydrogenated as before and hydrolyzed to give 5-hydroxy-7-azaindole (54%) and 6-hydroxy-7-azaindole (40%), the latter also predominating in the pyridone form.

Similar reactions were reported recently starting with 2-methyl-7-azaindole.<sup>70</sup> The intermediate 2-methyl-7-azaindoline was used to prepare 5-hydroxy-, 5-methoxy-, 5-benzyloxy-, and 5-dimethylamino-2-methyl-7-azaindole.

<sup>68</sup> M. M. Robison, F. P. Butler, and B. L. Robison, *J. Am. Chem. Soc.* **79**, 2573 (1957).

<sup>69</sup> M. M. Robison, B. L. Robison, and F. P. Butler, *J. Am. Chem. Soc.* **81**, 743 (1959).

<sup>70</sup> Merck and Co., Netherland Patent 6,510,648 (1966); *Chem. Abstr.* **65**, 13711 (1966).

This sequence is useful for preparing compounds inaccessible by other routes. It does, however, require reduction of the parent azaindole, obtained by one of the previously described methods. Also, it has been tried only on the 7 isomer, and it was reported that 5-azaindole is more resistant to reduction.<sup>18</sup>

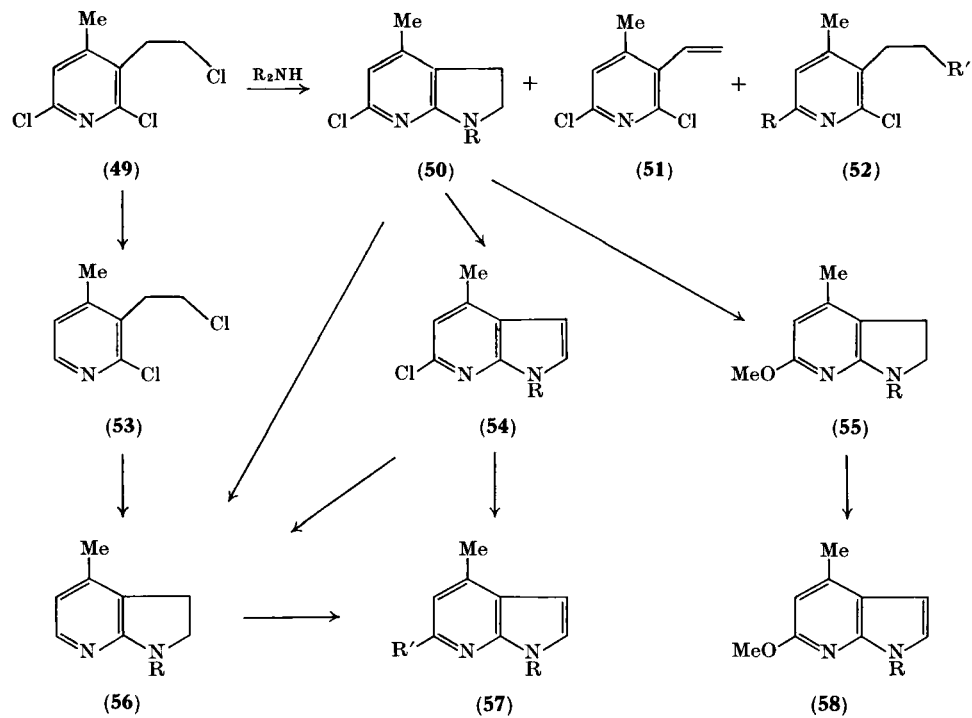
The most significant contributions to this approach have been made by Russian workers. Yakhontov and Rubtsov,<sup>71</sup> in 1960, reported a new type of ring closure by heating 2,6-dichloro-3-(2-chloroethyl)-4-picoline (**49**, Scheme 4) with secondary amines in chlorobenzene in sealed tubes to give 4-methyl-7-azaindolines (**50**). The  $\beta$ -collidine derivative (**49**) is readily obtained in four steps from  $\alpha$ -acetobutyrolactone.<sup>72</sup> The yield of azaindoline is dependent on the amine used and the reaction temperature. The reaction with dimethylamine at 140° gave a mixture of 54.5% of indoline (**50**, R = Me), 13% of the vinyl pyridine (**51**), and 31% of starting material (**49**). Use of *N*-methylaniline gave 1-phenylindoline (**50**, R = Ph) in 91% yield at 190°, whereas at 140° only starting material was recovered.<sup>71</sup> It was found that consistently higher yields of indoline were obtained with *N*-alkylanilines than with dialkylamines and with no formation of dehydrohalogenation product **51**, which was attributed to their lower basicity.<sup>73</sup> More recently, Yakhontov *et al.*<sup>74</sup> studied the effect of substituents in the *p*-position of *N*-methylaniline and aniline on the reaction and found electron-withdrawing groups lowered the yield of indoline. The reactions of the dichloro derivative **53** with *p*-methoxyaniline, *N*-methyl-*p*-dimethylamino-, *N*-methyl-*p*-cyano-, and *N*-methyl-*p*-nitroaniline gave the corresponding indolines (**56**, R = *p*-X-C<sub>6</sub>H<sub>4</sub>) in 85, 61, 26, and 24% yields, respectively. Reaction of collidine **53** with *p*-nitroaniline itself at 190° gave the azaindole (**57**, R = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>; R' = H) in 55% yield,<sup>74</sup> and with *N*-methylaniline

<sup>71</sup> L. N. Yakhontov and M. V. Rubtsov, *Zh. Obshch. Khim.* **30**, 3300 (1960); *J. Gen. Chem. USSR (English Transl.)* **30**, 3269 (1960). (The transliteration of the first letter of the first author's name to "Y" follows *Chem. Abstr.* policy. The Russian Journals translate it as "J" or "I", in which case it is indexed accordingly.)

<sup>72</sup> J. R. Stevens, R. H. Beutel, and E. Chamberlin, *J. Am. Chem. Soc.* **64**, 1093 (1942).

<sup>73</sup> L. N. Yakhontov and M. V. Rubtsov, *Zh. Obshch. Khim.* **34**, 493 (1964); *J. Gen. Chem. USSR (English Transl.)* **34**, 495 (1964).

<sup>74</sup> L. N. Yakhontov, D. M. Krasnokutskaya, and M. V. Rubtsov, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* p. 66 (1966); *Chem. Abstr.* **64**, 19582 (1966).



SCHEME 4

gave azaindoline **56** ( $R = Ph$ ) (90 %), also obtained by reduction of the 6-chloroindoline (**50**,  $R = Ph$ ) in 95 % yield.<sup>75</sup> With dibutylamine, the dichloro compound (**53**) gave a mixture of 1-butyldoline **56** ( $R = Bu$ ) (14 %), the vinyl product (11 %), and 2-chloro-3-(2-dibutylaminoethyl)-4-picoline (**52**,  $R = H$ ,  $R' = Bu_2N$ ) (8 %).<sup>75</sup> The trichlorocollidine (**49**) also gives a butyldoline (**50**,  $R = Bu$ ) (17 %) and vinyl picoline (**51**), but gives the 6-dibutylamino compound (**52**,  $R = Bu_2N$ ,  $R' = Cl$ ).<sup>76</sup> The butylazaindoline (**50**,  $R = Bu$ ) was obtained in 31 % yield from the trichloro compound (**49**) and butylamine at 190°, compared to 17 % with dibutylamine at 140°. <sup>77</sup> The cyclization of the dichloro derivative (**53**) was achieved also by conversion to 2-chloro-3-(2-hydroxyethyl)-4-picoline, which was heated with dibutylamine at 300° to give butyl-**56** ( $R = Bu$ ) and with *N*-methylaniline at 280° to give phenyl-**56** ( $R = Ph$ ) in 76 % yield.<sup>78</sup>

6-Chloro-4-methyl-7-azaindoline (**50**,  $R = H$ ) was obtained in 53 % yield by heating a 16:1 mole ratio of ammonia and trichlorocollidine (**49**) at 180° for 12 hours.<sup>79</sup> These conditions were optimum, with lower ratios and temperatures giving less product. The chloro compound (**50**,  $R = H$ ) was reduced quantitatively to 4-methyl-7-azaindoline (**56**,  $R = H$ ), which was converted to 1-acetyl and 1-alkyl derivatives (**56**,  $R = Ac$ ,  $CH_2Ph$ ,  $Bu$ ) in high yield. 6-Methoxyindoline (**55**,  $R = H$ ) was obtained in 77 % yield by the vigorous treatment of the chloroindoline (**50**,  $R = H$ ) with potassium methoxide in methanol in a sealed tube at 190°. These conditions with the butyl derivative (**50**,  $R = Bu$ ) gave azaindoline **55** ( $R = Bu$ ) in only 21 % yield. 1-Phenyl-**50** ( $R = Ph$ ) required a temperature of 250°, giving the indoline (**55**,  $R = Ph$ ) in 72 % yield.<sup>80</sup> Hydrolysis of these 6-methoxyazaindolines (**55**) with hydrochloric acid gave the 6-hydroxy compounds in good yield.<sup>80</sup>

<sup>75</sup> L. N. Yakhontov and M. V. Rubtsov, *Zh. Obshch. Khim.* **31**, 3281 (1961); *J. Gen. Chem. USSR (English Transl.)* **31**, 3062 (1961).

<sup>76</sup> L. N. Yakhontov and M. V. Rubtsov, *Zh. Obshch. Khim.* **34**, 1129 (1964); *J. Gen. Chem. USSR (English Transl.)* **34**, 1119 (1964).

<sup>77</sup> L. N. Yakhontov, M. S. Sokolova and M. V. Rubtsov, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, **74** (1966); *Chem. Abstr.* **64**, 19583 (1966).

<sup>78</sup> L. N. Yakhontov and M. V. Rubtsov, *Zh. Obshch. Khim.* **32**, 432 (1962); *J. Gen. Chem. USSR (English Transl.)* **32**, 425 (1962).

<sup>79</sup> L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, *Zh. Obshch. Khim.* **34**, 1449 (1964); *J. Gen. Chem. USSR (English Transl.)* **34**, 1454 (1964).

<sup>80</sup> L. N. Yakhontov, D. M. Krasnokutskaya, E. M. Peresleni, Ju. N. Sheinker, and M. V. Rubtsov, *Tetrahedron* **22**, 3233 (1966).

An important step in this sequence to azaindoles is dehydrogenation of the azaindoles. Initially, this was carried out by refluxing the indoline with chloranil in xylene, with 1-butylindoline (**56**, R = Bu) giving 1-butyl-4-methyl-7-azaindole (**57**, R = Bu, R' = H) in 47 % yield.<sup>75</sup> 6-Chloroazaindoline (**50**, R = H) was dehydrogenated similarly in 52 % yield,<sup>79</sup> and later this was improved to 80 % when refluxed for only 1.5 hours.<sup>81</sup> In an attempt to dechlorinate the resultant 6-chloroazaindole (**54**, R = H) to azaindole (**57**, R = R' = H) with hydrogen and palladium, only azaindoline (**56**, R = H) was isolated. The conversion proceeded smoothly, however, with lithium in liquid ammonia to give 4-methyl-7-azaindole (**57**, R = R' = H) in 69 % yield.<sup>79</sup> Difficulty was encountered in attempts to obtain this compound by dehydrogenation of azaindoline (**56**, R = H), with chloranil only resin being obtained. The 1-acetyl derivative (**56**, R = Ac) also failed with chloranil or selenium.<sup>79</sup> It was found that these dehydrogenations could be readily carried out by adding the azaindoline in toluene to sodium in liquid ammonia, which is then evaporated and the mixture boiled under reflux.<sup>82</sup> The unsubstituted azaindoline (**56**, R = H) and the 6-chloro- (**54**, R = H), 1-acetyl- (**56**, R = Ac), and 1-benzyl- (**56**, R = CH<sub>2</sub>Ph) indolines all gave 4-methyl-7-azaindole (**57**, R = R' = H) in 71, 77, 90, and 80 % yields, respectively. The methoxyazaindole (**58**, R = H) was obtained in 55 % yield from the corresponding azaindoline (**55**, R = H). This reaction failed if the nitrogen was substituted by a group (**56**, R = Bu or Ph) that was not readily replaced by sodium. In these cases, the chloranil procedure is required. Yakhontov *et al.*<sup>82</sup> extended this to ordinary indolines, indoline itself giving indole in 87 % yield. They<sup>83</sup> studied the course of the reaction, finding that the reflux period was not necessary if air was bubbled into the sodium-ammonia mixture, with the best yield for the parent (**57**, R = R' = H) being 83 %. Only 5–7 % was isolated if oxygen was excluded. The conversion was explained by the formation of the nitrogen sodio derivative which is oxidized by air.

The chloranil dehydrogenation of 1-phenylazaindoles is facilitated with electron-releasing substituents in the *p*-position, e.g., the *p*-methoxy compound (**57**, R = *p*-MeOC<sub>6</sub>H<sub>4</sub>, R' = H), being obtained in

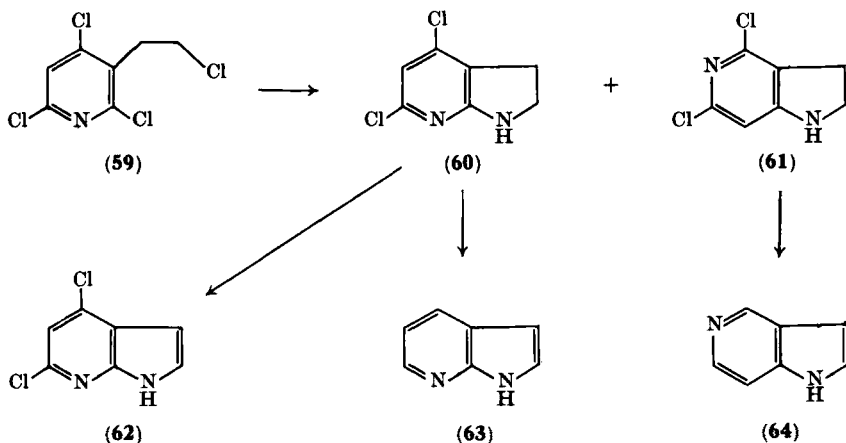
<sup>81</sup> L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, *Zh. Organ. Khim.* **1**, 2032 (1965); *J. Org. Chem. USSR (English Transl.)* **1**, 2072 (1965).

<sup>82</sup> L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, *Zh. Obshch. Khim.* **34**, 1456 (1964); *J. Gen. Chem. USSR (English Transl.)* **34**, 1460 (1964).

<sup>83</sup> L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, *Zh. Organ. Khim.* **1**, 2029 (1965); *J. Org. Chem. USSR (English Transl.)* **1**, 2069 (1965).

88 % yield.<sup>74</sup> Electron-withdrawing groups lower the reactivity. In fact, the *p*-nitrophenylazaindoline (**56**, R = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>) failed to dehydrogenate with chloranil, although with 2,3-dichloro-4,5-dicyanoquinone (DDQ) in refluxing xylene it did give some of the azaindole (20 %).

The 6-methoxyazaindolines (**55**, R = Bu, Ph) have been dehydrogenated with chloranil to give the methoxyazaindoles (**58**, R = Bu, Ph) in 82 and 91 % yield, respectively.<sup>83a</sup> The 6-hydroxyazaindoles were obtained in low yield (17–28 %) by acid hydrolysis of the methoxy derivatives (**58**, R = H, Bu, Ph).



SCHEME 5

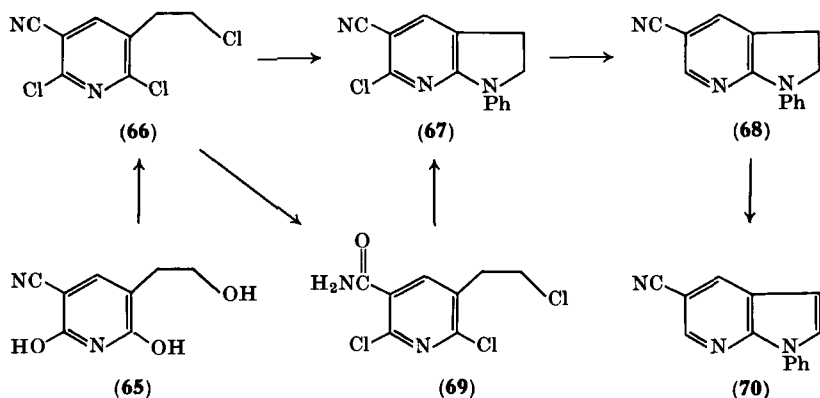
Routes to azaindoles without the 4-methyl group were also successful. 2,4,6-Trichloro-3-(2-chloroethyl)pyridine (**59**, Scheme 5), obtained in 79 % yield by treatment of the 4,6-dihydroxy compound with phosphoryl chloride at 180° in a bomb, was heated in a sealed tube at 180° with 20 % alcoholic ammonia to give a mixture of 4,6-dichloro-7-azaindoline (**60**) (35%) and 4,6-dichloro-5-azaindoline (**61**) (42 %), which were separated on alumina.<sup>84</sup> Sodium in liquid ammonia treatment gave 7-azaindole (**63**) in 45 % yield but only resin with **61**. It was reduced first to 5-azaindoline (97 %) which gave 5-azaindole (**64**) (80 %). Dehydrogenation of the 7 isomer (**60**) with DDQ in refluxing

<sup>83a</sup> L. N. Yakhontov, D. M. Krasnokutskaya, E. M. Peresleni, Yu. N. Sheinker, and M. V. Rubtsov, *Dokl. Akad. Nauk SSSR* **172**, 118 (1967); *Chem. Abstr.* **66**, 104506 (1967).

<sup>84</sup> L. N. Yakhontov, M. Ya. Urtskaya, and M. V. Rubtsov, *Khim. Geterotsikl. Soedin*; *Akad. Nauk Latv. SSR*, 918 (1965); *Chem. Abstr.* **64**, 17563 (1966).



xylene gave 4,6-dichloro-7-azaindole (**62**) in 71 % yield. These workers<sup>85</sup> also prepared 5-cyano-1-phenyl-7-azaindole (**70**, Scheme 6) starting with 2,6-dihydroxy-5-cyano-3-(2-hydroxyethyl)pyridine (**65**), obtained in 41 % yield overall by treatment of  $\gamma$ -butyrolactone with ethyl formate and sodium ethoxide followed by cyanoacetamide and ammonia. The chloroazaindoline (**67**) was obtained in 49 % yield directly from the trichloronitrile (**66**) (prepared as before in only 27 % yield) by heating with *N*-ethylaniline at 140°, or in 66 % from amide



SCHEME 6

**69**, the hydrolysis product of nitrile **66** (65 % yield). Dechlorination with hydrogen and palladium gave the cyanoazaindoline (**68**) (35 %), which was dehydrogenated to the azaindole (**70**) with chloranil in 50 % yield.

Yakhontov and Rubtsov<sup>86</sup> also prepared the interesting quaternary azaindolinium compound (**72**), by heating trichlorocollidine (**49**) with pyrrolidine to form the intermediate diamine (**71**), which was cyclized on further heating to the spiro derivative (**72**), isolated in 21 % yield. Similarly, trichlorocollidine (**53**) formed the indolinium compound (**73**) with piperidine.

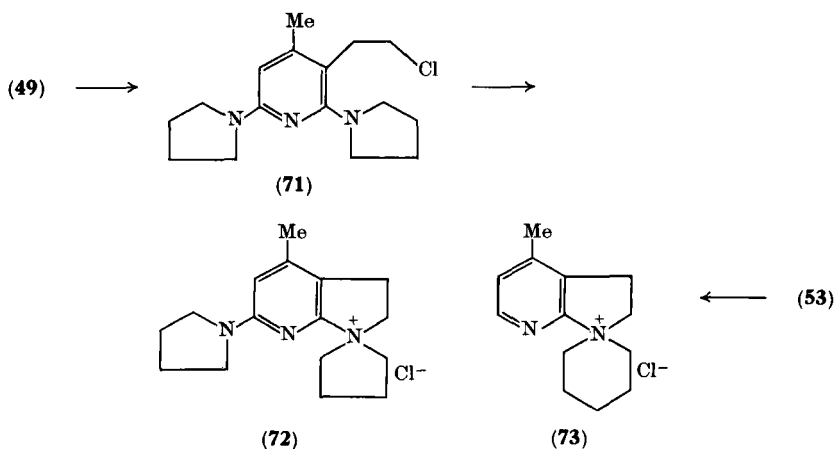
Recently it was reported that treatment of 3-(2-aminoethyl)pyridine with *n*-butyllithium, followed by heating the resultant

<sup>85</sup> L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, *Khim. Geterotsikl. Soedin.*, *Akad. Nauk Latv. SSR*, 59 (1966); *Chem. Abstr.* **64**, 17563 (1966).

<sup>86</sup> L. N. Yakhontov and M. V. Rubtsov, *Biol. Aktivn. Soedin.*, *Akad. Nauk SSSR* p. 90 (1965); *Chem. Abstr.* **64**, 5057 (1966).

*N*-lithio salt in dioxan, gives 7-azaindole.<sup>87</sup> The formation of the intermediate azaindoline was detected by gas chromatography.

The limitations of this approach to the synthesis of azaindoles are: (i) unavailability of other amino- or chloroethylpyridines suitable for cyclization; (ii) adaptation to the synthesis of the other azaindoles; and (iii) the necessity of high temperature and pressure for cyclization, requiring specialized equipment for large-scale preparations. For those applications already investigated it does offer a unique and useful method for the synthesis of a variety of 7-azaindole derivatives.



#### F. OTHER SYNTHESSES

In addition to the more conventional approaches discussed above, several attempts have been made to synthesize azaindoles by other routes, some of which have been successful. For convenience these have been separated into those leading directly to azaindoles (this section) and those involving oxygenated intermediates (Section III,G).

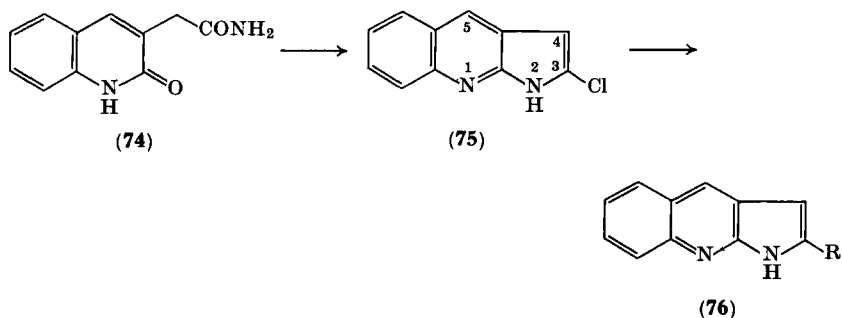
During their early investigations of harmine, Perkin and Robinson<sup>53</sup> attempted a synthesis of what they thought to be isoharman. The 2-quinolone amide (74) was cyclized with phosphoryl chloride to a chloro compound (75), which gave 2*H*-pyrrolo[2,3-*b*]quinoline (76, R = H) with tin and hydrochloric acid, and its 3-methyl derivative (76, R = Me) with methylmagnesium iodide. The name "quinindole"

<sup>87</sup> R. A. Abramovitch and J. B. Davis, unpublished results (1965); cited in Abramovitch and Saha (ref. 52) p. 345.

was suggested by these workers for this ring system. Application of this reaction to pyridones does not appear to have been made.

Bernstein *et al.*<sup>88</sup> synthesized 6-amino-2,3-diphenyl-7-azaindole (77) in 89% yield by heating nearly equimolar amounts of 2,6-diaminopyridine, its hydrochloride salt, and benzoin at 185°.

Cookson<sup>88a</sup> condensed 3-hydroxyimino-1-methyl-4-piperidone with ethyl acetoacetate in the presence of zinc to give ethyl 4,5,6,7-tetrahydro-2,6-dimethyl-6-azaindole-3-carboxylate, which was oxidized with mercuric acetate to the 6,7-dihydro compound.



Attempts at azaindole syntheses starting with the pyrrole ring have met with only limited success. Herz and Tocker<sup>89</sup> were able to cyclize the *N'*-acetyl and *N'*-benzoyl derivatives of 2-(2-aminoethyl)pyrrole with phosphoryl chloride in refluxing toluene to give 6,7-dihydro-4-methyl-5-azaindole (78, R = Me) and 6,7-dihydro-4-phenyl-5-azaindole (78, R = Ph) in 18 and 24% yields, respectively. Dehydrogenation with palladium on carbon in refluxing toluene gave the corresponding 4-methyl-5-azaindole (79, R = H) (84%) and 4-phenyl-5-azaindole (79, R = Ph) (86%). No product could be isolated from the reaction with the *N'*-formyl compound. These workers<sup>5</sup> also investigated application of the Pomeranz-Fritsch reaction to the cyclization of 2-pyrrole iminoacetals (80). They were able to obtain 6-azaindole (81, R = R' = H), apoharmine (81, R = Me, R' = H), and 1-methyl-6-azaindole (81, R = H, R' = Me) in 2.2, 5.1, and 27% yields, respectively, by heating the suitable acetal (80) with a mixture of polyphosphoric acid and phosphoryl chloride at 120°. Besides the azaindoles, the

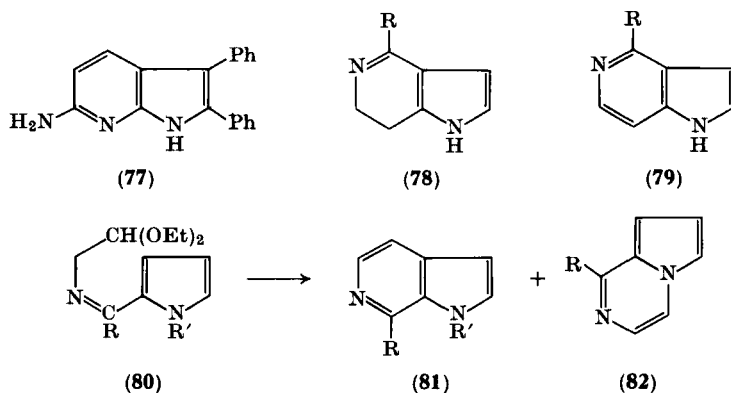
<sup>88</sup> J. Bernstein, B. Stearns, E. Shaw, and W. A. Lott, *J. Am. Chem. Soc.* **69**, 1151 (1947).

<sup>88a</sup> G. H. Cookson, *J. Chem. Soc.*, 2789 (1953).

<sup>89</sup> W. Herz and S. Tocker, *J. Am. Chem. Soc.* **77**, 6353 (1955).

aldehyde (**80**,  $R = R' = H$ ) and acetyl derivatives (**80**,  $R = Me$ ,  $R' = H$ ) gave rise to pyrrolo[1,2-*a*]pyrazine (**82**,  $R = H$ ) (21 %) and its 1-methyl derivative (**82**,  $R = Me$ ) (23 %). The use of polyphosphoric acid gave lower, but more reproducible, results.

Herz and Murty<sup>20</sup> tried a similar cyclization with *N*-(3-pyridyl)-aminoacetal and its *N*-oxide, but the former gave an intractable tar



and the latter decomposed immediately with polyphosphoric acid.

Attempts to condense 4-methylamino- and 4-phenylamino-nicotinic acid 1-oxides with glycollic aldehyde, as in the Harley-Mason indole synthesis, failed.<sup>62</sup>

Reisch<sup>90</sup> obtained 7-azaindole in 54 % yield by heating 3-ethynylpyridine with sodium amide in ammonia-saturated pseudocumenol at 170–180° for 16 hours, 2-amino-3-ethynylpyridine being formed as an intermediate.

Interestingly, 7-azaindole is formed in the pyrolysis of nicotine at or above 800°. <sup>91</sup> It was considered a free radical reaction and unusual as it involves a three-atom rather than a four atom side chain in the cyclization. Quinoline is also formed. The products were identified by gas chromatography.

All efforts to prepare 4- and 6-azaindole by the reductive cyclization of 3-nitro-2- and 3-nitro-4-pyridylecyanoacetates were unsuccessful. <sup>92</sup>

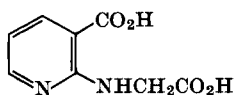
<sup>90</sup> J. Reisch, *Chem. Ber.* **97**, 2717 (1964).

<sup>91</sup> C. H. Jarboe and G. J. Roseme, *J. Chem. Soc.*, 2455 (1961).

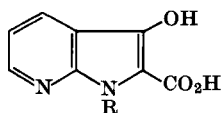
<sup>92</sup> R. E. Willette, *J. Chem. Soc.*, 5874 (1965).

## G. SYNTHESIS OF OXYGENATED DERIVATIVES

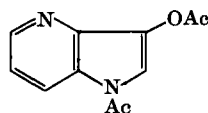
Many of the early investigators looking for superior indigo dyes turned their attention to pyridine analogs, which were called "pyrindigos." Sucharda<sup>93</sup> condensed 2-aminonicotinic acid with chloroacetic acid to form the diacid **83**, which cyclized on heating in water or acid to give 7-azaindoxylic acid<sup>94</sup> (**84**, R = H). This structure was criticized by Tschitschibabin,<sup>94a</sup> whose work with 2-aminopyridine led him to formulate it as a pyrazolo[1,2-*a*]pyridine, i.e., with cyclization onto the ring nitrogen. Sucharda<sup>95</sup> later agreed with this suggestion although he rightly pointed out that there was no direct



(83)



(84)



(85)

proof for either structure. Treatment of the diacid **83** with acetic anhydride and potassium acetate gave, instead of the expected *O,N*-diacetylindoxyl, the *N*-acetyl derivative of **84** (R = Ac).<sup>92</sup> Attempts to hydrolyze or reduce this compound failed. Sucharda<sup>95</sup> also cyclized the isomeric 3-(carboxymethyl)-aminopicolinic acid to a "pyrindoxyl acid," which was not isolated but oxidized directly to 4,4'-diazaindigo, or "δ-pyrindigo." In this case, with acetic anhydride and potassium acetate, the expected 3-acetoxy-1-acetyl-4-azaindole (**85**) was obtained in 63% yield.<sup>92</sup> This azaindoxylic derivative is unstable, readily darkening on exposure to air, and decomposing with a variety of reagents.

Reindel<sup>96</sup> reported the synthesis of 7,7'-diazaindigo by oxidation of the sodium salt of 7-azaindoxyl, for which he ascribed structure **86** or **87**, and it was prepared in near quantitative yield by heating *N*-(2-pyridyl)aminoacetic acid with 30% sodium hydroxide. The

<sup>93</sup> E. Sucharda, *Roczniki Chem.* **3**, 236 (1923); *Chem. Abstr.* **19**, 72 (1925).

<sup>94</sup> According to *Chemical Abstracts*: 3-Hydroxy-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid. The common names indoxyl, oxindole, and isatin will be used as they do not imply which tautomer is predominant. It is noted that the tautomers shown are in accord with current theory for indoles and have not been established as such.

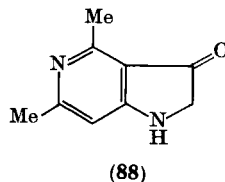
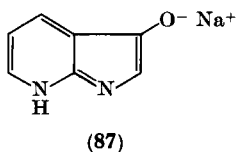
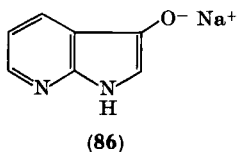
<sup>94a</sup> A. E. Tschitschibabin, *Chem. Ber.* **57**, 2092 (1924).

<sup>95</sup> E. Sucharda, *Chem. Ber.* **58**, 1724 (1925).

<sup>96</sup> F. Reindel, *Chem. Ber.* **57B**, 1381 (1924).

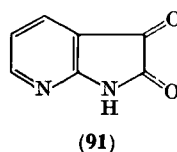
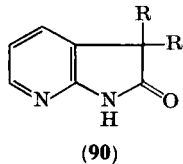
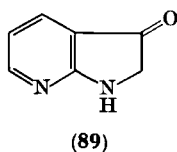
possibility of the sodium salt being that of an imidazolo[1,2-*a*]pyridine, which would result from cyclization onto the pyridine nitrogen, was ruled out on the basis of the solubility of the monobenzoyl and insolubility of the dibenzoyl derivatives in alkali.

4,6-Dimethyl-5-azaindoxyl (**88**) was obtained in 30% yield by



refluxing 4-(carboxymethyl)amino-2,6-dimethylnicotinic acid with acetic anhydride followed by hydrolysis with alkali.<sup>97</sup>

An interesting sequence to some of these compounds was reported by Kägi<sup>98</sup> starting with 2-amino-3-diazoacetylpyridine, prepared from 2-aminonicotiny chloride and diazomethane in 77% yield.<sup>99</sup> Attempts to cyclize the diazoketone to 7-azaindoxyl (**89**) failed, but it did rearrange with aniline at 180° to give 7-azaaxindole (**90**, R=H) in 62% yield. Diazotization gave the 3-oxime (94%), which was



hydrolyzed to 7-azaisatin (**91**) in 73% yield. Hydrolysis of the diazoketone with dilute sulfuric acid gave 7,7'-diazaindigo in 20% yield.

In 1953, Cookson<sup>100</sup> reported the cyclization of porphobilinogen (**92**, R=H) to give the pyrrole lactam (**93**, R=H), a derivative of 4,5,6,7-tetrahydro-6-azaindol-5-one. Jackson *et al.*<sup>101</sup> synthesized the diacid (**93**, R=CO<sub>2</sub>H) from the triacid (**92**, R=CO<sub>2</sub>H) by a different route, then decarboxylated it to the lactam (**93**, R=H) in 80%

<sup>97</sup> E. Koenigs and H. Kantrowitz, *Chem. Ber.* **60**, 2097 (1927).

<sup>98</sup> H. Kägi, *Helv. Chim. Acta* **24**, 141E (1941).

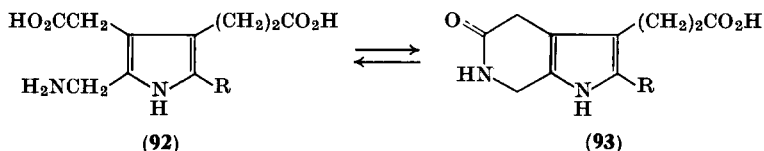
<sup>99</sup> K. Miescher and H. Kägi, *Helv. Chim. Acta* **24**, 1471 (1941).

<sup>100</sup> G. H. Cookson, *Nature* **172**, 457 (1953).

<sup>101</sup> A. H. Jackson, D. M. McDonald, and S. F. McDonald, *J. Am. Chem. Soc.* **78**, 505 (1956).

yield. Hydrolysis of this to porphobilinogen (**92**, R = H) constitutes a synthesis of this interesting compound.

Okuda and Robison<sup>41</sup> prepared 7-azaoxindole (**90**, R = H) in 67 % yield by heating 2-aminopyridine-3-acetic acid at 225° under nitrogen. Their<sup>18</sup> attempts to synthesize 5-azaoxindole from 3-bromo-4-acetamidopyridine by creation of an intermediate "pyridyne" species were unsuccessful. Ficken and Kendall<sup>102</sup> obtained a small amount of 3,3-dimethyl-7-azaoxindole (**90**, R = Me) by heating 1-isobutyryl-2-(2-pyridyl)hydrazine with calcium oxide. They were



unsuccessful in attempts to prepare azaoxindoles by heating *N*-methyl-2-(2-bromo-2-methylpropionyl)aminopyridine with aluminium chloride or 2-methylaminopyridine with glyoxal sodium bisulfite.

Hooper *et al.*<sup>20a</sup> synthesized 2-phenyl-6-azaisatogen (3-keto-3*H*-pyrrolo[2,3-*c*]pyridine 1-oxide) from 3-nitro-4-phenylethynylpyridine by treatment with nitrosobenzene. The 2-*p*-dimethylaminophenyl-4- and -6-azaisatogens were prepared from 2- and 4-*p*-dimethylamino-styryl-3-nitropyridines, respectively, by irradiation with sunlight. The yields of all three were low.

To date, none of the above syntheses appears to be a suitable route to nonoxygenated azaindole derivatives.

## IV. Chemical Properties

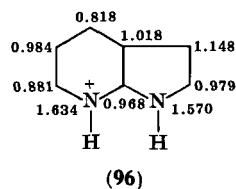
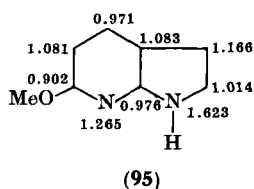
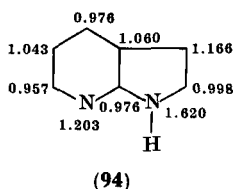
### A. GENERAL

Fusion of an electron-withdrawing or  $\pi$ -deficient pyridine ring with an electron-releasing or  $\pi$ -excessive pyrrole ring to form an azaindole gives a system which retains certain chemical properties of both rings, but, expectedly, of a lower order of reactivity. The pyrrole ring is attacked by electrophilic reagents in the 3-position like indole, although with greater difficulty. A few nucleophilic substitution

<sup>102</sup> G. E. Ficken and J. D. Kendall, *J. Chem. Soc.*, 747 (1961).

reactions have been reported where a halogen on the pyridine ring is displaced, but no example of hydrogen being substituted by a nucleophilic reagent has been recorded.

The  $\pi$ -electron density diagram of 7-azaindole (94), calculated by the LCAO-MO method by Bochvar *et al.*,<sup>103</sup> is in agreement with experimental results. Because the electron densities at the 3-position in 7-azaindole (94) and 6-methoxy-7-azaindole (95) are the same and only slightly less than those calculated for indole (1.170) and 6-methoxyindole (1.169), these investigators explain the lowered reactivity toward electrophilic reagents by the formation of the protonated form of 7-azaindoles (96). They state the order of ease of electrophilic substitution for 4-methyl-7-azaindoles is 6-Cl > 6-H >



6-MeO, and suggest that substituents in this position may affect the ability to protonate the nitrogen. This is not in complete agreement with the expected order of basic strength, i.e., 6-H ( $pK_a$  5.23<sup>23</sup>) > 6-MeO (estimated  $pK_a$  ca. 3) > 6-Cl (ca. 1), although the weakly basic 6-chloro compound is claimed to be the more reactive. Actually, the differences in reactivity, if based on isolated yields, are not great for nitration or bromination, whereas the 6-methoxy compound does give a much lower yield on cyanomethylation.

The  $\pi$ -electron diagrams also illustrate that the electron density in the pyridine ring is greater than in pyridine itself, accounting for its increased resistance to nucleophilic attack. This is evidenced by the difficulty with which the 6-chloro compounds undergo substitution reactions or reduction, and by failure of the 4-methyl group to condense with aldehydes or to be oxidized.<sup>103</sup>

<sup>103</sup> D. A. Bochvar, A. A. Bogatur'yants, A. V. Tutkevich, L. N. Yakhontov, M. Ya. Uritskaya, D. M. Krasnokutskaya, and M. V. Rubtsov, *Izv. Akad. Nauk SSR, Ser. Khim.*, 354 (1966); *Bull. Acad. Sci. USSR, Div. Chem. Sci. (English Transl.)*, 327 (1966).



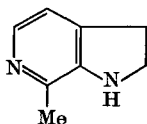
The electron density on the pyrrole nitrogen atom in 7-azaindole is a little lower than in indole; however,  $N_{(1)}$  acylation of the azaindoles proceeds readily under mild conditions.<sup>104</sup>

The relative reaction rates of a variety of substituted azaindoles have not been studied quantitatively, making further speculations risky. Other differences in reactivity will be discussed under the appropriate reactions. A detailed study of the effect of the azanitrogen's position on chemical properties is glaringly lacking, which is probably due in part to the unavailability of some of the azaindoles.

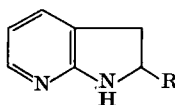
In general, the azaindoles are stable, colorless, high-melting solids with little, if any, odor. They fail to give a positive test with Ehrlich's reagent or the pine-splint reaction. Also in contrast to indoles, they are stable to boiling mineral acids and darken on exposure to air very gradually. Like pyrroles and indoles, they are stable to aqueous alkaline solutions.

#### B. REDUCTION AND OXIDATION

Azaindoles are more resistant to reduction than indoles, but under more rigorous conditions do add 1 mole of hydrogen to give 2,3-dihydroazaindoles, i.e., azaindolines.



(97)



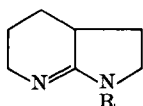
(98)

Fischer<sup>2</sup> treated apoharmine with phosphorus and hydroiodic acid to obtain a dihydro compound, which appears to be 7-methyl-6-azaindoline (97), as it gave a *N*-nitroso derivative with nitrous acid. The first catalytic hydrogenation studies were made by Kruber,<sup>6</sup> who obtained 7-azaindoline (98, R = H) in 81% yield by heating 7-azaindole with Raney nickel in decalin at 200° under 118 atm of hydrogen for 4 hours. Higher temperatures (250–270°) gave a tetrahydro product, which he thought to be 4,5,6,7-tetrahydro-7-azaindole. Robison *et al.*<sup>68</sup> later repeated this work and established that the

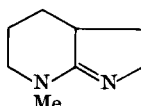
<sup>104</sup> For discussion of the pitfalls of using  $\pi$ -electron density and/or delocalization energy calculations for predictive purposes in pyridines and indoles, see J. Ridd, *Phys. Methods Heterocyclic Chem.* 1, 109 (1963); see also Abramovitch and Saha (ref. 52) p. 230.

tetrahydro compound they obtained was 2-amino-3-ethylpyridine. Although there are some discrepancies between the melting points of the picrate and dibenzoyl derivatives of the two reports, it seems likely they both isolated the pyridine.

Clemons and Swan<sup>21</sup> found that 2-methyl- and 2-ethyl-7-azaindole were reduced more reliably with copper chromite as catalyst under 160 atm of hydrogen at 180°. 2-Methyl-7-azaindoline (**98**, R = Me) was obtained in 42% yield. They reported that Kruber's conditions gave mostly gums, from which only a little of the *N*-benzoyl derivatives could be isolated. Recently, however, 2-methyl-7-azaindoline (**98**, R = Me) was prepared on a 0.7-mole scale by use of Raney nickel under conditions identical to those used by Kruber, although no yield was reported.<sup>70</sup>



(99)



(100)

7-Azaindole took up 3 moles of hydrogen at atmospheric pressure and 25° when stirred with Adams catalyst in acid solution to give 2,3,3a,4,5,6-hexahydro-7-azaindole (**99**, R = H) in 76% yield.<sup>68</sup> The amidine structure (**99**) agrees with its basic strength ( $pK_a$  ca. 11.7) and with comparison of its infrared spectrum to those of methyl hexahydro compounds **99** (R = Me) and **100**, obtained by reduction of 1-methyl-7-azaindole (28%) and 7-methyl-7*H*-7-azaindole (68%). Also, the amidine (**99**, R = H) gave a 1-phenylcarbamyl derivative with phenyl isocyanate (93% yield), but a dibenzoyl derivative with benzoyl chloride. If the reduction with Adams catalyst was carried out under neutral conditions,<sup>27</sup> the 7-methylazaindole consumed 5 moles of hydrogen to give 1-methyl-3-(2-aminoethyl)piperidine in 68% yield. Similarly, 1-methyl-7-azaindole-7-methiodide gave 1-methyl-3-(2-methylaminoethyl)piperidine (50%).<sup>68</sup>

Interestingly, 5-azaindole resists atmospheric-pressure hydrogenation with Adams catalyst in acidic medium.<sup>18</sup> Also, 7-azaindole and its 1-ethoxycarbonyl derivatives are recovered from treatment with lithium aluminum hydride.<sup>68</sup> This reagent readily reduced the dihydropyridine ring of 6,7-dihydro-4-methyl-7-azaindole to the corresponding 4,5,6,7-tetrahydro compound in 83% yield.<sup>89</sup>

As noted above (Section III,E), attempts to remove the chloro

group in 6-chloro-4-methyl-7-azaindole (**54**, R = H) with palladium and hydrogen led to 4-methyl-7-azaindoline.<sup>79</sup> Removal of chlorine is carried out best with lithium or sodium in ammonia. Other reactions of the compounds were also discussed above.

Azaindoles are more stable to air oxidation than indoles, are stable to mild reagents like silver oxide and selenium dioxide, but are readily attacked by permanganate. In the structure proof of 7-azaindole, Kruber<sup>6</sup> oxidized the 1-benzenesulfonyl derivative with potassium permanganate in acetone solution to obtain 2-(benzenesulfonyl)aminonicotinic acid. The 1-acetyl and 1-benzoyl derivatives gave inconsistent results, which Kruber attributed to their ease of hydrolysis. 1-Benzoyl-2,5-dimethyl-4-azaindole and its 3-substituted derivatives give 3-benzamido-6-methylpicolinic acid with permanganate oxidation.<sup>16</sup>

### C. ELECTROPHILIC SUBSTITUTION

#### 1. Nitration

Azaindoles are nitrated readily by treatment with fuming nitric acid at 0°. In his early work, Fischer<sup>105</sup> nitrated apoharmine, obtaining a high-melting crystalline compound, which reacted with methyl iodide and alkali, to give, presumably, 3-nitro-6,7-dimethyl-6*H*-6-azaindole.<sup>106</sup> The stepwise decarboxylation of harminic acid gives a monocarboxylic acid, 7-methyl-6-azaindole-2-carboxylic acid, which was also nitrated. The position of nitration was not established in either case.

Good evidence for nitration at the 3-position was provided by Clayton and Kenyon.<sup>16</sup> 1-Benzoyl-2,5-dimethyl-4-azaindole was nitrated in 60% yield, and followed with potassium permanganate oxidation in aqueous acetone gave 3-benzamido-6-methylpicolinic acid. Alkaline hydrolysis of the nitration product gave 3-nitro-2,5-dimethyl-4-azaindole (85% yield), which was also obtained by direct nitration of 2,5-dimethyl-4-azaindole in low yield. In addition, reduction gave the 3-amino compound, which was identical to that obtained by catalytic reduction of the product formed by coupling the azaindole with benzenediazonium chloride.

3-Nitro-7-azaindole was obtained in 83% yield at 0°, and was reduced to the 3-amino compound, which is unstable as the free base,

<sup>105</sup> E. Fischer, *Chem. Ber.* **30**, 2481 (1897).

<sup>106</sup> E. Fischer and C. Buck, *Chem. Ber.* **38**, 329 (1905).

and was isolated as the dihydrochloride.<sup>69</sup> Nitro and other electron-withdrawing substituents in the 3-position increase the acidity of the azaindoles so that they are soluble in dilute alkali and insoluble in dilute acid.<sup>69, 107</sup>

The series of unsubstituted, 6-chloro-, and 6-methoxy-4-methyl-7-azaindoles were nitrated at  $-10^{\circ}$  to give the corresponding 3-nitro compounds in 56, 57, and 60 % yield, respectively.<sup>81</sup> At  $0^{\circ}$ , the methoxy isomer gave what appeared to be the 1,3-dinitro compound, which decomposed explosively on heating.

## 2. Bromination

Bromination proceeds readily with azaindoles to give a monobromo compound, whereas pyrrole and indoles react violently to give poly-halogenated products.

Fischer<sup>2</sup> attempted the bromination of apoharmine in dilute sulfuric acid at room temperature and obtained a "tetrabromo" compound, which he did not characterize further. Treatment of 1-benzoyl-2,5-dimethyl-4-azaindole with bromine in acetic acid at  $25^{\circ}$  gave the 3-bromo-1-benzoyl compound in 60 % yield. On oxidation with permanganate it gave the same picolinic acid obtained before.<sup>16</sup> Alkaline hydrolysis gave 3-bromo-2,5-dimethyl-4-azaindole (90 %), also obtained by direct bromination of 2,5-dimethyl-4-azaindole in 60 % yield.

Bromination of 7-azaindole in chloroform at  $0^{\circ}$  gave 3-bromo-7-azaindole in 81 % yield.<sup>107</sup> This compound is stable to treatment with sodium iodide in acetone, like 3-bromoindole, and with hot dilute hydrochloric acid, whereas the indole undergoes hydrolysis.

Yakhontov *et al.*<sup>81</sup> also brominated the 4-methyl-7-azaindoles, using bromine in chloroform or bromine-dioxan, obtaining high yields of the brominated 6-H (82 %), 6-Cl (82 %), and 6-MeO (71 %) compounds. The ultraviolet spectra of these compounds agrees with the assignments of the bromine to the 3-position.

## 3. Mannich Reactions

The Mannich reaction with azaindoles is of great importance as it leads to azagramines, which are useful as intermediates. Unfortunately, almost all of the work has been done with 7-azaindoles.

<sup>107</sup> M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.* **78**, 1247 (1956).

Robison and Robison<sup>22</sup> were the first to prepare 7-azagramine (3-dimethylaminomethyl-7-azaindole), finding the following procedure to give optimum yields. The azaindole, 10% excess dimethylamine hydrochloride, and one molar equivalent of paraformaldehyde are refluxed together in *n*-butanol for 30 minutes, followed by evaporation under reduced pressure. The residue is extracted with dilute acid, from which the base is precipitated with sodium carbonate. This procedure has been used with only minor variations on a variety of 7-azaindoles. Williamson<sup>108</sup> obtained 7-azagramine in 99% yield on a 0.2-mole scale, compared to 81%.<sup>22</sup> Other 7-azagramines prepared similarly are: 1-phenyl-4-methyl (72%),<sup>109</sup> 1-butyl-4-methyl (64%),<sup>77</sup> 6-chloro-4-methyl (60%),<sup>81</sup> 4-methyl (28%),<sup>81</sup> 2-methyl,<sup>70</sup> and 5-methyl (60%).<sup>24</sup> In the case of the last two 4-methyl compounds, it was found that the best yields were obtained with use of a 3:1 molar ratio of dimethylamine hydrochloride and only a 15-minute reflux period.<sup>81</sup> With the 6-chloro-4-methyl isomer, some (6%) of the bis-(7-aza-3-indolyl)methylene by-product was formed.

Several modifications of the Mannich reaction were tried with 5-azaindole, but no isolatable product could be obtained.<sup>18</sup> Since the Mannich conditions are usually acidic (pH 5–7),<sup>109a</sup> it seems the difference in reactivity between 5- and 7-azaindole can be accounted for by the greater basic strength ( $pK_a$  8.26<sup>14</sup>) of the former compared to the latter ( $pK_a$  4.59<sup>14</sup>). As noted above, protonation of the pyridine nitrogen has the effect of lowering the electron availability at the 3-position. Under the conditions of the reaction 5-azaindole would exist almost entirely in the protonated form (**101**), which is stabilized by resonance with the *para*-quinonoid canonical form (**102**), thus lowering the electron density of the pyrrole ring further. Protonation of 7-azaindole would be only partial, with mostly neutral molecule present. Also, the *ortho*-quinonoid form (**104**) of the protonated species (**103**) is unimportant (see Section V,B,2).

<sup>108</sup> W. R. N. Williamson, *J. Chem. Soc.*, 2833 (1962).

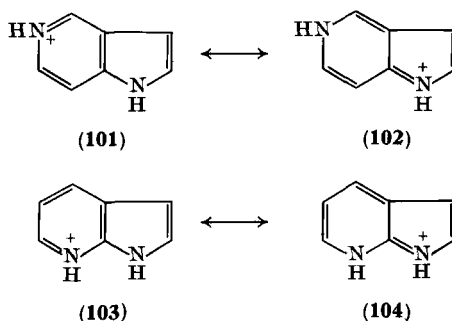
<sup>109</sup> L. N. Yakhontov and M. V. Rubtsov, *Zh. Obshch. Khim.* **34**, 2603 (1964); *J. Gen. Chem. USSR (English Transl.)* **34**, 2626 (1964).

<sup>109a</sup> If the amine salt is not used in the Mannich Reaction, acid is usually added to keep the pH acidic enough to maintain the formaldehyde liberated, although no detailed study of the effects of pH on the course of the reaction could be found. The apparent pH of the butanol reaction mixture described above was 6.80, with 7-azaindole, before and after the reflux period. The mixture was taken to dryness and the residue dissolved in the same volume of water. The pH of the aqueous solution was 6.75.

Some *N*-substituted 5-azagramines have been described but no synthesis is given.<sup>109b</sup>

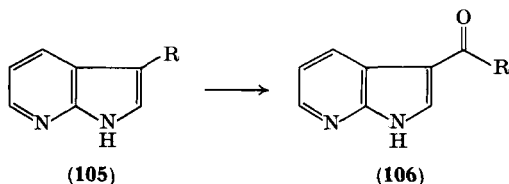
Frydman *et al.*<sup>66</sup> reported the synthesis of ethyl 5-methoxy-6-azagramine-2-carboxylate, isolated in 75% yield as the dihydrochloride.

The reactions of the azagramines are discussed below (Section IV,F,1).



#### 4. Acylation on Carbon

The most useful acylation reaction of azaindoles, as with indoles, is 3-formylation. This is carried out conveniently with the Vilsmeier reagent (phosphoryl chloride in dimethylformamide).



Carbonation of the sodium salt of 7-azaindole (105, R=H) gives 7-azaindole-3-carboxylic acid (106, R=OH) in low yield.<sup>6, 107</sup> Robison and Robison<sup>107</sup> also prepared it from 7-azaindole-3-carboxaldehyde (105, R=CHO) either by direct oxidation (28% yield) or through the oxime, which was dehydrated with acetic anhydride to 1-acetyl-3-cyano-7-azaindole. This compound was hydrolyzed in water to give 3-cyano-7-azaindole (105, R=CN); in refluxing hydrochloric acid it

<sup>109b</sup> Sterling Drug Inc., Belgian Patent 659,467 (1965); *Chem. Abstr.* **64**, 2098 (1966).

gave the acid (**106**, R=OH) (37 %); and in ethanolic hydrogen chloride it gave the ethyl ester (**106**, R=OEt) (65 %), which was saponified to the acid (**106**, R=OH) (75 %).

In an attempt to expand the pyrrole ring with dichlorocarbene, Clemo and Swan<sup>21</sup> treated 2-methyl-7-azaindole with chloroform and potassium hydroxide, but isolated mostly starting material and a small amount of the 3-carboxaldehyde. Similarly, 2,5-dimethyl-4-azaindole-3-carboxaldehyde was obtained in 36 % yield.<sup>16</sup>

The Vilsmeier reagent gave 3-carboxaldehydes of 1-phenyl- (76 %),<sup>109</sup> 1-butyl- (48 %),<sup>77</sup> and 6-chloro- (25 %)<sup>81</sup> 4-methyl-7-azaindoles. The aldehydes can also be obtained from the gramines, and this is the way in which 7-azaindole- and 4-methyl-7-azaindole-3-carboxaldehydes were prepared (see Section IV,F,1).

### 5. Alkylation on Carbon

The treatment of 2,5-dimethyl-4-azaindole with ethyl magnesium bromide, followed by benzyl chloride, gave 3-benzyl-2,5-dimethyl-4-azaindole.<sup>16</sup> Cyanomethylation of 6-unsubstituted, 6-chloro-, and 6-methoxy-4-methyl-7-azaindole with potassium cyanide and formalin in ethanol at 120° gave the corresponding ethyl 3-acetates in 30, 32, and 3 % yields, respectively.<sup>81</sup> No nitrile-containing product was isolated.

Several (7-aza-3-indolyl)acetonitriles were prepared by various methods including treatment of the azaindole in DMF with sodium hydride followed by chloroacetonitrile.<sup>109b</sup> Also, 4-, 5-, 6-, and 7-azaindoles gave the corresponding 2- and 3-indolyl- $\beta$ -propionitriles when heated with acrylonitrile.

Intramolecular cyclization of some 7-azatryptamine derivatives is discussed in Section IV,F,5.

### 6. Miscellaneous

2,5-Dimethyl-4-azaindole was found to couple with benzene-diazonium chloride to give the 3-phenylazo compound in 70 % yield.<sup>16</sup> It was reduced to the unstable 3-amine which was isolated as 1-acetyl-3-acetamido-2,5-dimethyl-4-azaindole. The same compound was obtained by reduction of the nitration product of the parent. A small amount of 3-phenylazo-7-azaindole was obtained under similar conditions.<sup>107</sup>

## D. NUCLEOPHILIC SUBSTITUTION

As with pyrroles and indoles, examples of nucleophilic substitution of azaindoles are rare. 7-Azaindole was treated with sodamide in several solvents, with only starting material or decomposition products being isolated.<sup>69</sup> 6-Chloro-4-methyl-7-azaindole undergoes exchange with hydriodic acid in a sealed tube at 170–190° to give 6-iodo-4-methyl-7-azaindole in 34% yield, and with potassium methoxide at 300° to give 6-methoxy-4-methyl-7-azaindole in 39% yield.<sup>79</sup> Lower temperatures in the latter reaction gave greatly reduced yields. Replacement of the chloro group by hydrogen was discussed above (Section IV,B).

The only example of nucleophilic substitution in the pyrrole ring is the treatment of the chloropyrroloquinoline (75) with methyl magnesium iodide or tin and hydrochloric acid (nucleophilic substitution by hydride).<sup>53</sup> However, the structures of these three compounds have never been rigorously proved.

## E. REACTIONS INVOLVING THE NITROGEN ATOMS

1. *Acylation on Nitrogen*

Azaindoles are readily acylated on the pyrrole nitrogen by warming on a water bath with acid anhydrides or with acid chlorides in the presence of carbonate or pyridine. Good yields were obtained by this procedure for the following compounds: 1-acetyl-7-azaindole,<sup>6, 21</sup> 1-benzoyl- and 1-benzenesulfonyl-7-azaindole,<sup>6</sup> 1-benzoyl-2-methyl-7-azaindole,<sup>21</sup> 1-ethoxycarbonyl- and 1-chloroacetyl-7-azaindole,<sup>68</sup> 1-acetyl-3-cyano-7-azaindole,<sup>107</sup> 1-benzoyl-4-azaindole,<sup>13</sup> and 1-acetyl- and 1-benzoyl-2,5-dimethyl-4-azaindole.<sup>16</sup> The only reported failure was with 5-methyl-2-phenyl-4-azaindole, which failed to react with acetic anhydride or benzoyl chloride.<sup>16</sup> 2-Methyl-7-azaindole-3-acetic acid was acylated by treatment of its *tert*-butyl ester with sodium hydride in dimethylformamide, followed by *p*-chlorobenzoyl chloride.<sup>70</sup>

No example of *N*-acylation of 5- or 6-azaindoles appears to have been recorded.

The 1-acylazaindoles are hydrolyzed easily with alkali and are relatively stable to acids at low temperatures. At least in one case, the 3-cyano compound, hydrolysis proceeds readily with water.<sup>107</sup>



## 2. Alkylation on Nitrogen

*N*-Alkylation of azaindoles at the 1-position is carried out as with indoles and aminopyridines, i.e., treatment of the sodio derivative with alkyl halide in an organic solvent. Refluxing xylene is required for the azaindoles.

Protiva *et al.*<sup>17</sup> formed the sodium salt of 2-methyl-5-phenyl-4-azaindole with sodamide in xylene and refluxed it with  $\beta$ -dimethyl-aminoethyl chloride to obtain the 1-alkylated compound. Robison *et al.*<sup>68</sup> found with 7-azaindole that use of sodium hydride in xylene, followed by refluxing with methyl iodide, gave 1-methyl-7-azaindole in 62% yield, compared with only 19% when sodamide was used.<sup>27</sup> Also, in the latter case, they isolated a small amount of 7-azaskatole and suspected traces of the 7-methyl compound to be present.

Several 1-alkanonitriles of 4-, 5-, 6-, and 7-azaindole were prepared in a similar manner.<sup>109b</sup>

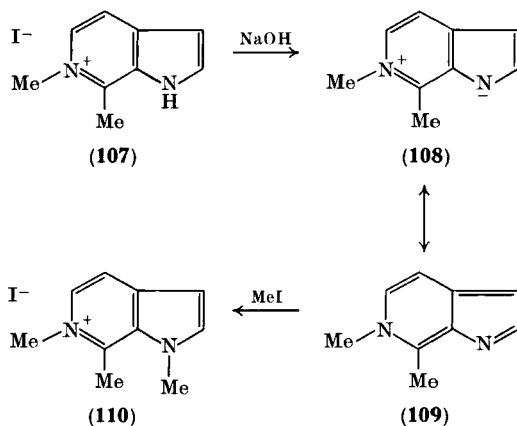
## 3. Alkylation Involving Quaternization

Azaindoles are quaternized with ease on treatment with methyl iodide, methylation occurring on the pyridine nitrogen in a manner analogous to 2- and 4-aminopyridine.

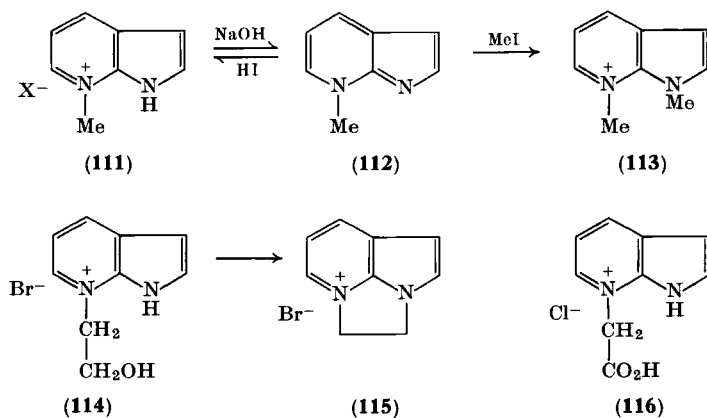
Apoharmine forms a methiodide<sup>107</sup> on warming with methyl iodide, losing the elements of hydriodic acid on treatment with alkali.<sup>105</sup> 3-Nitroapoharmine was found to react in the same way.<sup>106</sup> Schwarz and Schlittler<sup>110</sup> studied the ultraviolet spectral data of these compounds and several related  $\beta$ -carboline methiodides, suggesting the methiodide structure (107). The free base, 6,7-dimethyl-6-azaindole, was considered to exist in the resonance forms  $108 \leftrightarrow 109$ , although the 6*H* form (109) seems a suitable representation, as forms with separation of charges in a neutral molecule. (i.e., 108) contribute little to its stability. The free base (109) was allowed to react with methyl iodide to give the di-*N*-methyl salt (110).<sup>110</sup> The ultraviolet spectra of these and the following compounds are discussed in Section V.B,2.

A similar series of reactions was carried out with 7-azaindole.<sup>27</sup> The 7-methyl salt (111) was obtained in quantitative yield as the iodide (111, X = I) by allowing 7-azaindole to stand with methyl iodide at room temperature for 4 days. Methyl *p*-toluenesulfonate in

<sup>110</sup> H. Schwarz and E. Schlittler, *Helv. Chim. Acta* **34**, 629 (1951).



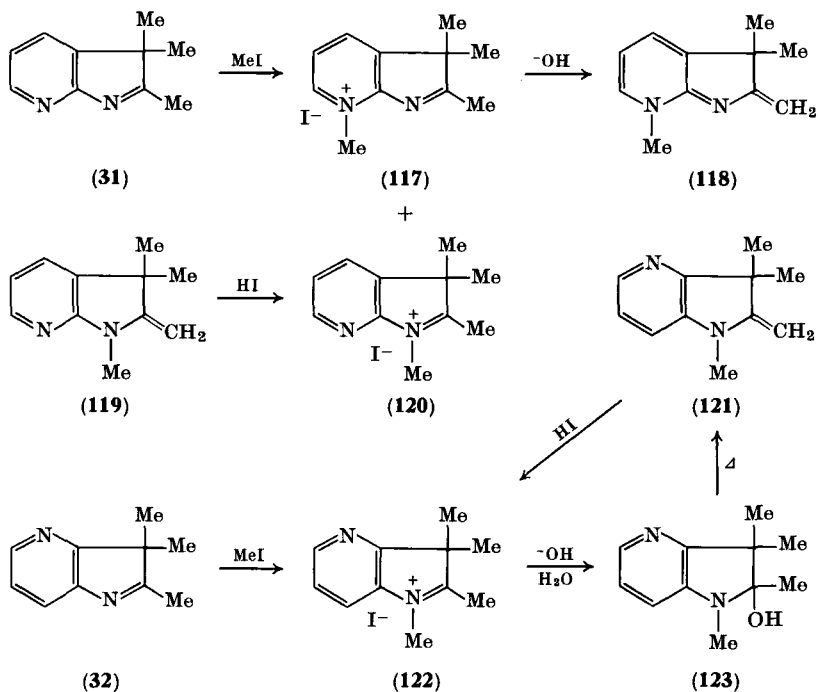
refluxing benzene gave the *p*-toluenesulfonate salt (**111**, X =  $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_3$ ) in 93% yield. With a saturated solution of potassium carbonate, these gave 7-methyl-7H-7-azaindole (**112**). On treatment with hydriodic acid the original salt (**111**, X = I) was obtained. The 7-methyl compound (**112**) resists hydrolysis in boiling 20% sodium



hydroxide, whereas 1-methyl-2-pyridoneimine is readily hydrolyzed to the pyridone. Further treatment of **112** with methyl iodide at room temperature gave 1-methyl-7-azaindole 7-methiodide (1,7-dimethyl-1H-pyrrolo[2,3-b]pyridinium iodide) (**113**), also obtained in better purity from 1-methyl-7-azaindole in the same manner.

7-Methyl-7-azaindolum iodide (**111**,  $X=I$ ) was also prepared by Saxena<sup>110a</sup> in addition to the 7-benzyl and 7-*p*-nitrobenzyl salts. These all gave anhydro bases (e.g. **112**).

Robison *et al.*<sup>68</sup> prepared the 7-(2-hydroxyethyl) salt (**114**) in 88 %

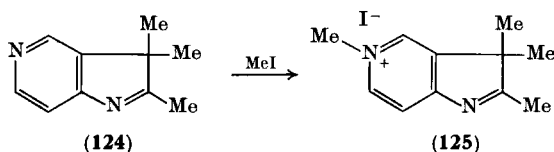


SCHEME 7

yield by heating a mixture of 7-azaindole and 2-bromoethanol on a steam bath for 1.5 hours. Treatment of this salt with phosphorous tribromide in xylene at 0° followed by refluxing gave the cyclization product (**115**), named as 1,7-ethano-1*H*-pyrrolo[2,3-*b*]pyridinium bromide. The 7-carboxymethyl salt (**116**) was obtained from 1-chloroacetyl-7-azaindole on exposure to air over a month period or by boiling it in water.<sup>68</sup>

<sup>110a</sup> J. P. Saxena, *Indian J. Chem.* **5**, 73 (1967).

Ficken and Kendall<sup>50, 51</sup> studied the formation and reactions of quaternary salts of azaindolenines (Scheme 7). Reaction of 2,3,3-trimethyl-7-azaindolenine (**31**) with methyl iodide gave the 7-methiodide (**117**) in 57% yield.<sup>50</sup> Although the 1-methiodide (**120**) could not be isolated, some 5–10% of it was found to be present. The 1-methiodide (**120**) was prepared unambiguously by Fischer cyclization of methyl ethyl ketone 1-methyl-1-(2-pyridyl)hydrazone to the anhydro base (**119**), followed by hydriodic acid. The ultraviolet spectra of the 7-methiodide (**117**) was similar to that of base **31** in acid solution, as were the spectra of the 1-methiodide (**122**) and 1,2,3,3-tetramethylindolenine iodide in alkaline solution. In contrast, the 7-methiodide (**117**) gave a spectrum in alkaline medium that was greatly shifted, and can be accounted for by formation of the 2-methylene-*o*-quinonoid structure (**118**). These studies indicate that N<sub>(7)</sub> is more basic than N<sub>(1)</sub> in the 7-azaindolenines (cf. Section V,A).



In the case of the 4-azaindolenine (**32**), however, methylation gave the 1-methiodide (**122**), but it was felt that some of the 4-methiodide was probably formed, as the yield was low (50%).<sup>51</sup> With *N* sodium hydroxide, the 1-methiodide (**122**) added water to give the pseudobase (**123**), which was dehydrated on heating, forming the methine base (**121**). Prepared also as before by Fischer cyclization of the 3-pyridylhydrazone, it added hydrogen iodide to give the 1-methiodide (**122**), thereby providing proof of structure **122**. The possibility of this salt existing in a tautomeric form, i.e., as structure **121** protonated on N<sub>(4)</sub>, was discounted by the fact that the 2-methyl group of the methiodide was very reactive in forming cyanine dyes. Infrared spectral data of the free bases were in agreement with their structures.

The 5-azaindolenine (**124**) was reported to quaternize almost exclusively on the pyridine nitrogen atom, to give methiodide (**125**), although no evidence is given.<sup>51, 111</sup> Since the azaindolenines do not

<sup>111</sup> G. E. Ficken and J. D. Kendall, British Patent 841,588 (1960); *Chem. Zentr.* **133**, 18344 (1962).

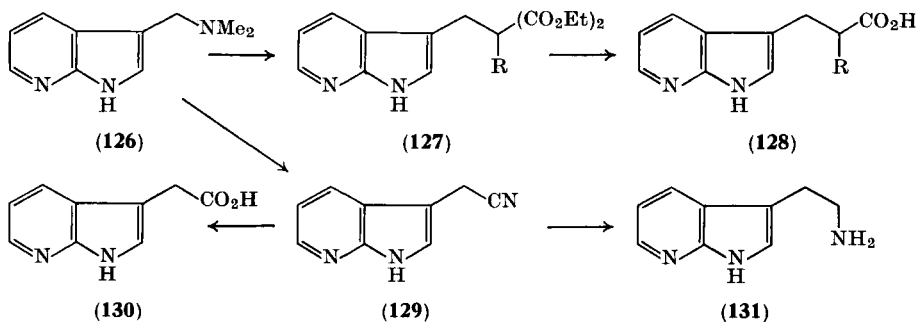
possess an aromatic pyrrole ring, their reactions with methyl iodide tend to parallel those of the aminopyridines, i.e., 7- and 5-azaindolenine being alkylated mainly on the ring nitrogen like 2- and 4-aminopyridine, and the 4-aza isomer on the imine nitrogen like 3-aminopyridine.<sup>112</sup>

## F. REACTIONS INVOLVING SIDE CHAINS

In general, the side chain derivatives of azaindoles undergo reactions analogous to those with indoles. The azagramines and 3-carboxaldehydes are the most useful, leading to many other azalogs of indole derivatives of biological importance. Unfortunately, most of the reactions and compounds involve the more accessible 7-azaindoles, so few comparisons in reactivity differences can be made.

### 1. Reactions of Azagramines

7-Azagramine (**126**, Scheme 8) was condensed with diethyl acetamidomalonate in refluxing xylene in the presence of sodium



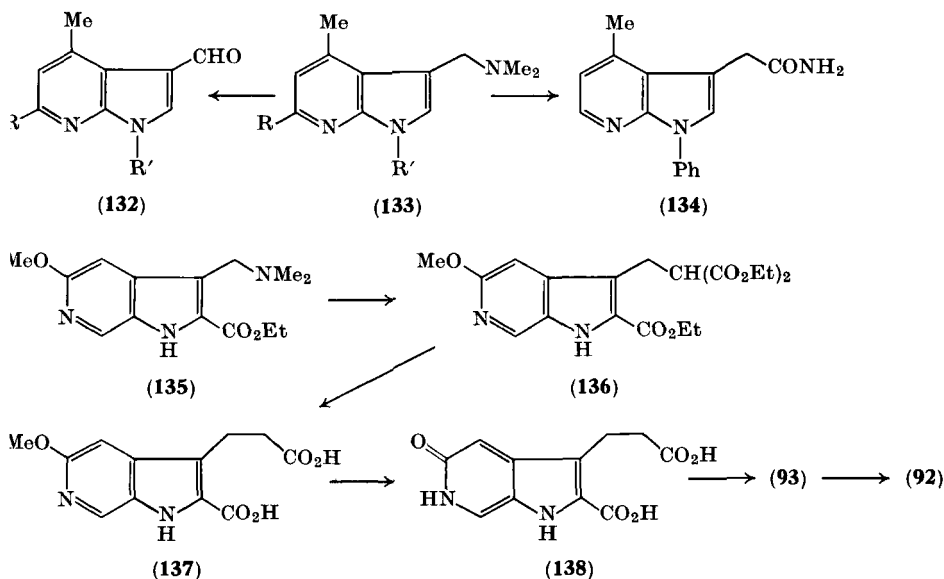
SCHEME 8

hydroxide to give the amide diester (**127**, R = NHAc) (72%), which was hydrolyzed and decarboxylated in refluxing hydrochloric acid to give 7-azatryptophan (**128**, R = NH<sub>2</sub>) in 85% yield.<sup>23</sup> 5-Methyl-7-azatryptophan was prepared in the same manner.<sup>24</sup> The nitro diester (**127**, R = NO<sub>2</sub>) (41%) was obtained by refluxing 7-azagramine and

<sup>112</sup> For further discussion of the quaternization, see G. F. Duffin, *Advan. Heterocyclic Chem.* **3**, 38 (1964).

diethyl nitromalonate in xylene.<sup>107</sup> Heating a mixture of 7-azagrame and diethyl malonate with a catalytic amount of sodium afforded the diester (**127**, R=H) (51 %), which gave  $\beta$ -(7-aza-3-indolyl)propionic acid (**128**, R=H) in 76 % yield on hydrolysis.<sup>107</sup>

Treatment of the azagrame (**126**) with sodium cyanide led to resins, but use of hydrogen cyanide (formed *in situ* with NaCN/HCl) in water with refluxing gave the 3-acetonitrile (**129**) in 49 % yield.<sup>107</sup> This has been prepared in better yield (76 %) by treatment of **126** with dimethyl sulfate followed by potassium cyanide.<sup>113</sup> The nitrile (**129**)



was reduced to 7-azatryptamine (**131**) with Adams catalyst and hydrochloric acid in ethanol (54 %)<sup>107</sup> or with Raney nickel in methanolic ammonia (85 %).<sup>113</sup> Hydrolysis of the nitrile (**129**) gave the 3-acetic acid (**130**) in 89 % yield.<sup>107</sup> 2-Methyl-7-azaindole-3-acetic acid was synthesized in a similar manner.<sup>70</sup>

Refluxing a mixture of 7-azagrame (**126**) and hexamethylenetetramine in propionic acid gave 7-azaindole-3-carboxaldehyde (**139**, Scheme 9) in 55 % yield.<sup>107, 108</sup> The 4-methyl-7-azagramines (**133**) were treated similarly to give the following 3-carboxaldehydes **132**:

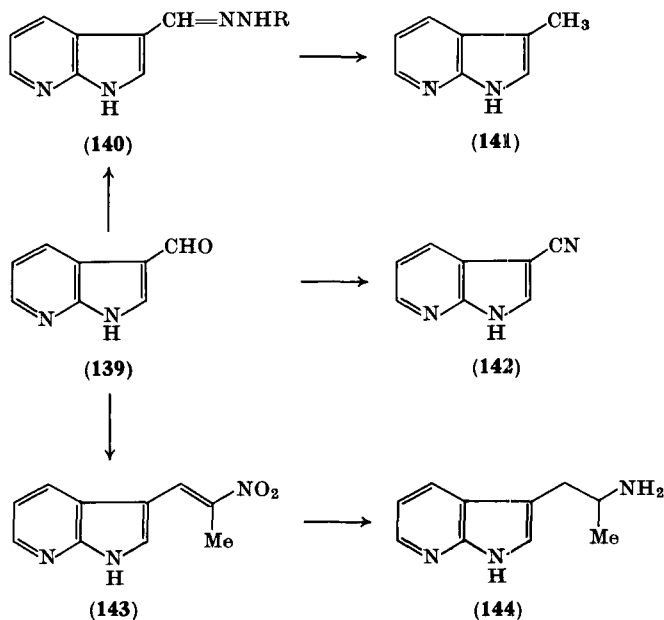
<sup>113</sup> L. Velluz, G. Muller, and A. Allais, French Patent 1,261,179 (1961); *Chem. Abstr.* **57**, 2274 (1962).

$R = R' = H$  (25 %),<sup>81</sup>  $R = Cl$ ,  $R' = H$  (69 %),<sup>81</sup>  $R = H$ ,  $R' = Bu$  (25 %),<sup>77</sup> and  $R = H$ ,  $R' = Ph$  (42 %).<sup>109</sup> The 1-phenyl gramine (**133**,  $R = H$ ,  $R' = Ph$ ) gave only a little of the 3-acetamide (**134**) and unchanged gramine, but no nitrile, on heating with hydrogen cyanide in water at 120° in a sealed tube.<sup>114</sup>

Frydman *et al.*<sup>66</sup> condensed ethyl 5-methoxy-6-azagramine-2-carboxylate (**135**) with diethyl sodiomalonate to give the triester (**136**) (80 %), which was hydrolyzed with hydrochloric acid to the diacid (**137**) (95 %). Treating this with hydrobromic acid gave the 5-hydroxy-6-azaindole, which exists in the lactam form (**138**). Reduction to the tetrahydrolactam (**93**,  $R = CO_2H$ ), followed by decarboxylation and hydrolysis, provided a novel route to porphobilinogen (**92**,  $R = H$ ).

## 2. Reactions of Azaindole-3-carboxaldehydes

7-Azaindole-3-carboxaldehyde (**139**, Scheme 9) formed a phenylhydrazone (**140**,  $R = Ph$ ) and semicarbazone (**140**,  $R = CONH_2$ ) in



SCHEME 9

<sup>114</sup> L. N. Yakhontov and M. V. Rubtsov, *Biol. Aktivn. Soedin., Akad. Nauk SSSR* p. 83 (1965); *Chem. Abstr.* **64**, 5057 (1966).

high yield.<sup>22</sup> Wolff-Kishner reduction of the latter gave 7-azaskatole (**141**) in 55% yield. The oxime of aldehyde **139** was dehydrated with acetic anhydride to give 1-acetyl-3-cyano-7-azaindole, which with water gave nitrile **142**.<sup>107</sup> This has been prepared directly from the aldehyde by refluxing it with diammonium hydrogen phosphate and nitropropane in glacial acetic acid for 16 hours.<sup>115</sup> A yield of 31% was obtained.

Boiling a mixture of aldehyde **139**, nitroethane, and ammonium acetate for 45 minutes gave a nitropropenyl compound (**143**) (89%), which was reduced to  $\alpha$ -methyl-7-azatryptamine (**144**) with lithium aluminium hydride in 55% yield.<sup>108</sup>

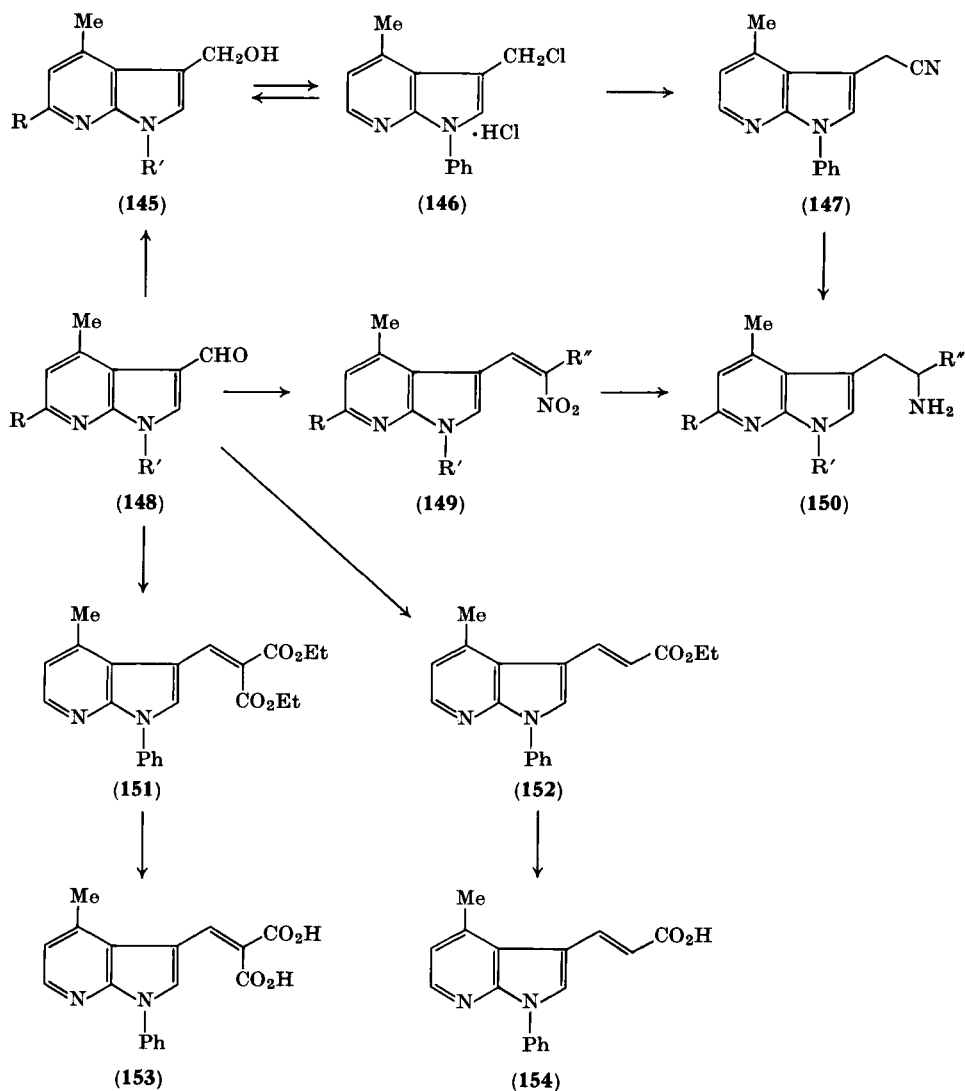
1-Phenyl-4-methyl-7-azaindole-3-carboxaldehyde (**148**, R = H, R' = Ph; Scheme 10) was reduced with sodium borohydride to the 3-hydroxymethyl compound (**145**, R = H, R' = Ph) in quantitative yield,<sup>109</sup> whereas the 6-chloro compound (**145**, R = Cl, R' = H) was obtained in only 10% yield.<sup>81</sup> Treatment of **145** (R = H, R' = Ph) with thionyl chloride gave the 3-chloromethyl compound (**146**), isolated in 99% yield as the hydrochloride.<sup>109</sup> With sodium bicarbonate in water, the 3-chloromethyl salt (**146**) is hydrolyzed rapidly back to the hydroxymethyl compound (**145**). An attempt to synthesize the 3-acetonitrile (**147**) by heating the 3-chloromethyl salt (**146**) with sodium cyanide in ethanol produced only the bisazaindolylmethylene ether (50%).<sup>114</sup> Use of acetone cyanohydrin gave the acetonitrile (**147**) (50%). It was hydrolyzed to give 1-phenyl-4-methyl-7-azaindole-3-acetic acid in 91% yield.<sup>114</sup>

Several of the 4-methyl-7-azaindole-3-carboxaldehydes (**148**) were condensed with nitroalkanes (MeNO<sub>2</sub>, EtNO<sub>2</sub>, and PrNO<sub>2</sub>) as described above to give the 3-(2-nitrovinyl) compounds (**149**, R = H, Cl; R' = H, Me, Et) in 33 to 84% yields.<sup>77, 109, 114, 116</sup> Many of these were reduced with lithium aluminum hydride to give the following 4-methyl-7-azatryptamines **150**: R = R' = R'' = H (74%),<sup>116</sup> R = Cl, R' = H, R'' = Me (84%),<sup>116</sup> R = Cl, R' = H, R'' = Et (91%),<sup>116</sup> R = R'' = H, R' = Bu (78%),<sup>77</sup> and R = H, R' = Ph, R'' = H (67%), Me, Et.<sup>114</sup> Under these conditions 6-chloro-3-(2-nitrovinyl)-4-methyl-7-azaindole (**149**, R = Cl, R' = R'' = H) was reduced to 4-methyl-7-azaskatole (3,4-dimethyl-7-azaindole).<sup>116</sup>  $\alpha$ -Methyl- (**150**, R = R' = H,

<sup>115</sup> H. M. Blatter, H. Lukaszewski, and G. DeStevens, *J. Am. Chem. Soc.* **83**, 2203 (1961).

<sup>116</sup> L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, *Zh. Organ. Khim.* **1**, 2040 (1965); *J. Org. Chem. USSR (English Transl.)* **1**, 2079 (1965).



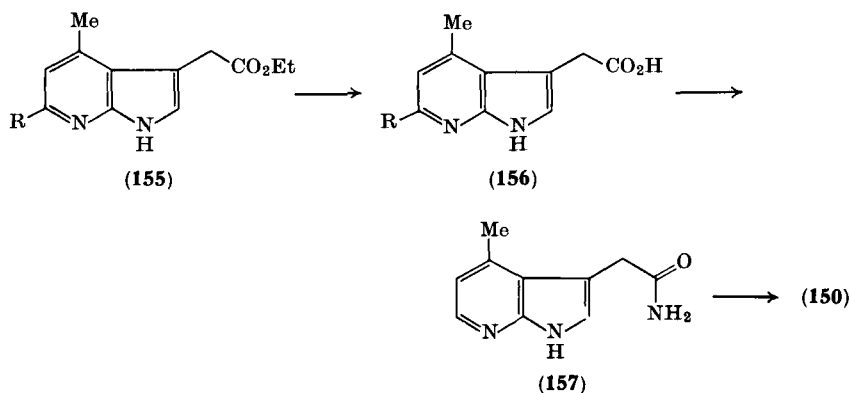


SCHEME 10

$R'' = \text{Me}$ ) and  $\alpha$ -ethyl- (150,  $R = R' = \text{H}$ ,  $R'' = \text{Et}$ ) -4-methyl-7-azatryptamine were obtained in nearly 50% yield by treatment of the corresponding 6-chloro compound with sodium in ammonia.<sup>116</sup> 1-Phenyl-4-methyl-7-azatryptamine (150,  $R = R'' = \text{H}$ ,  $R' = \text{Ph}$ ) was

obtained also by reduction of the 3-acetonitrile (**147**) with Raney nickel and hydrazine.<sup>114</sup>

The 1-phenyl 3-carboxaldehyde (**148**, R = H, R' = Ph) underwent reaction at 20° with diethyl malonate in ether, to which one drop of piperidine was added, to give the methylenemalonate (**151**) (90 %).<sup>109</sup> Alkaline hydrolysis gave the diacid (**153**) (70 %), which was decarboxylated in refluxing hydrochloric acid to the  $\beta$ -acrylic acid (**154**) (83 %). A Wittig reaction of the aldehyde (**148**, R = H, R' = Ph) with triethyl phosphonoacetate and sodium ethoxide in DMF at 10° gave the ethyl acrylate (**152**, 46 %), which was hydrolyzed also to the acid (**154**) (78 %).<sup>109</sup>



The oximes of the 1-butyl and 1-phenyl aldehydes (**148**) were reduced with zinc and hydrochloric acid to give 1-butyl-<sup>77</sup> and 1-phenyl-3-aminomethyl-4-methyl-7-azaindole,<sup>114</sup> in 63 and 65 % yield, respectively. Reduction of the 1-phenyl oxime with lithium aluminum hydride, however, was accompanied by reduction of the pyrrole ring to give the corresponding 3-aminomethyl azaindoline in 80 % yield.<sup>109</sup>

The 1-phenyl 3-carboxaldehyde, was found to resist oxidation with silver oxide or selenium dioxide, but was destroyed with permanganate.<sup>109</sup> It was recently converted to 1-phenyl-4-methyl-7-azaindole-3-acetic acid and 1-phenyl-4-methyl-7-azatryptophan via its azlactone derivative.<sup>116a</sup>

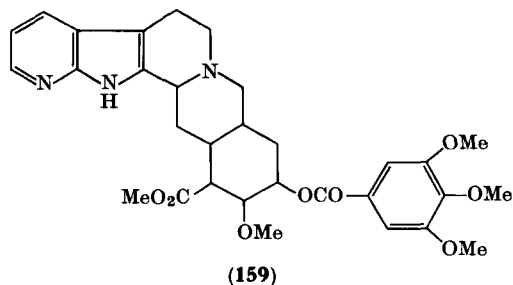
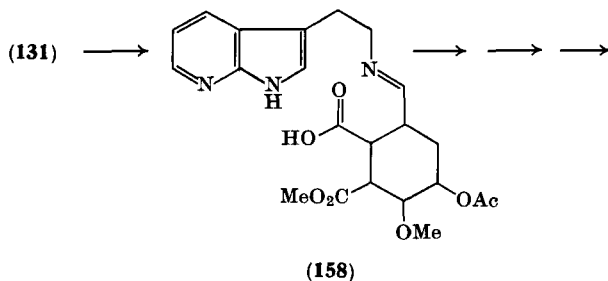
<sup>116a</sup> L. N. Yakhontov and M. V. Rubtsov, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 141 (1967).

### 3. Reactions of Ethyl Azaindole-3-acetates

Ethyl 4-methyl-7-azaindole-3-acetate (**155**, R = H), obtained from the attempted cyanomethylation of the indole, was hydrolyzed to the 3-acetic acid (**156**, R = H) (54 %), which was treated in succession by thionyl chloride and ammonia to give the 3-acetamide (**157**) (78 %).<sup>81</sup> Reduction with lithium aluminium hydride gave the azatryptamine (**150**, R = R' = R'' = H) in 94 % yield.<sup>116</sup> The 6-chloro ester (**155**, R = Cl) was hydrolyzed also to the acid (**156**, R = Cl.)<sup>81</sup>

### 4. Reactions of Azaindolyalkanonitriles

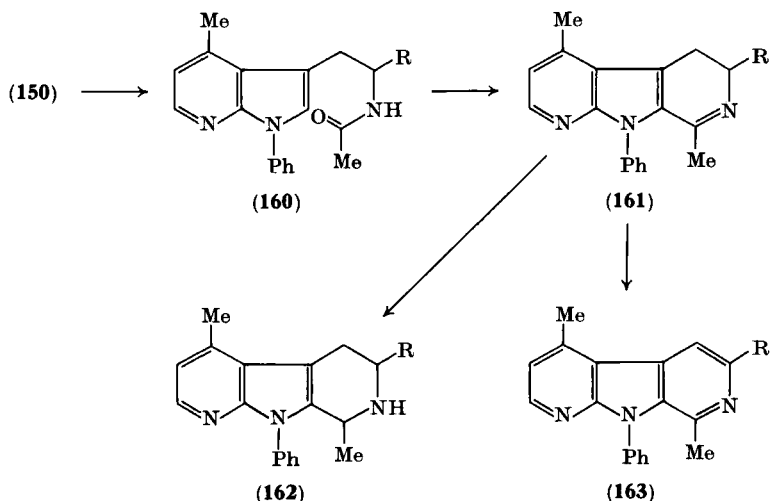
As mentioned above, (7-aza-3-indolyl)acetonitrile (**129**) was reduced catalytically to give 7-azatryptamine (**131**).<sup>107, 113</sup> Other 7-azatryptamines prepared similarly are: 1-methyl, 1-benzyl, 2-methyl, and 1-(2-aminoethyl).<sup>109b</sup> This patent also describes several other 1-, 2-, and 3-(aminoalkyl) derivatives of the four azaindole isomers. The several 4-, 5-, 6-, and 7-azaindolyalkanonitriles were also treated with hydroxylamine to give amidoximes and with hydrogen chloride in chloroform, followed by ammonia to give amidines.<sup>109b</sup>



## 5. Reactions of Azatryptamines

Velluz *et al.*<sup>113</sup> condensed 7-azatryptamine (**131**) with the 6 $\beta$ -formylcyclohexane derivative used in the reserpine synthesis to give the imine (**158**). This was reduced with sodium borohydride, heated to form the lactam, which was cyclized onto the pyrrole ring with phosphoryl chloride. This was followed by a number of steps to lead to 12-azadeserpidine (**159**).

An interesting series of compounds was synthesized from the 1-phenyl-4-methyl-7-azatryptamines (**150**) discussed above.<sup>117</sup> The acetamides (**160**, R = H, Me, Et; Scheme 11) were prepared in ca. 75 %

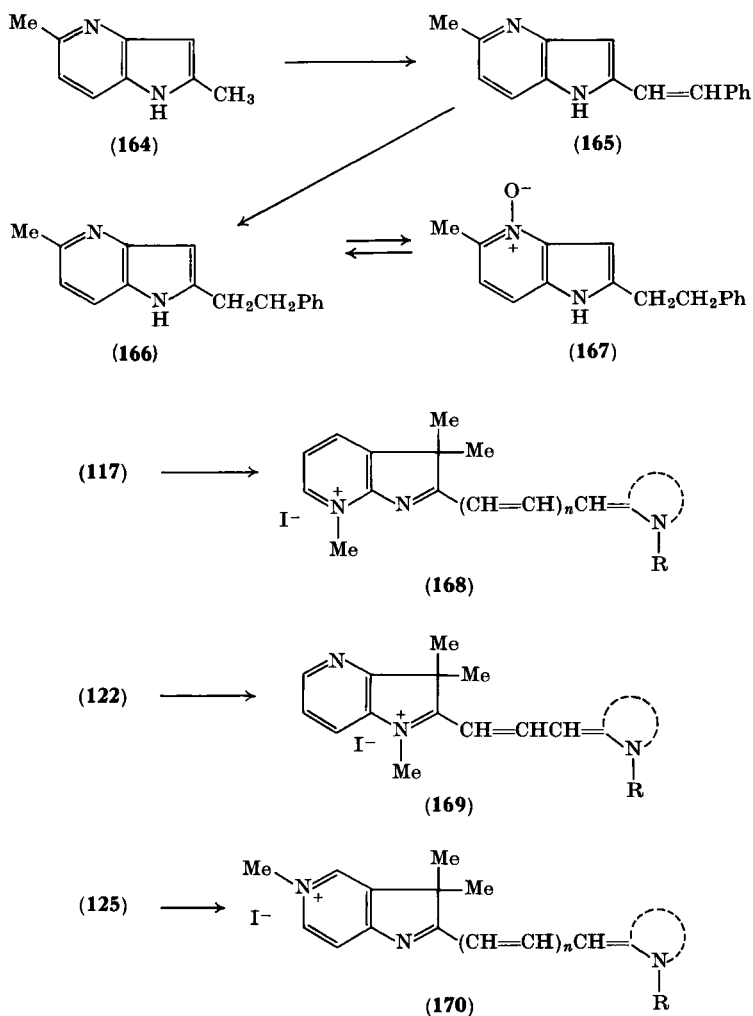


SCHEME 11

yield by allowing the amines to stand in acetic anhydride overnight. These were cyclized by heating with phosphoryl chloride to give the novel 5,6-dihydro-1,7-diazacarbazoles (**161**, R = H, Me, Et) in ca. 65 % yield. Sodium borohydride reduction gave the tetrahydro compounds (**162**, R = H, Me, Et) in ca. 75 % yield. The dihydro compound (**161**,

<sup>117</sup> L. N. Yakhontov and M. V. Rubtsov, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 80 (1966); *Chem. Heterocyclic Compds., Acad. Sci. Latv. SSR (English Transl.)* 2, 58 (1966).

R = H) was dehydrogenated with palladium black in refluxing xylene to give, in 73% yield, 5-methyl-9-phenyl-8-azaharman (163).<sup>118</sup>



<sup>118</sup> Named incorrectly as a 12-aza- $\beta$ -carboline derivative in *Chem. Abstr.* **64**, 19584 (1966). According to *Chem. Abstr.*, numbered as a carboline derivative it should be 7-aza- $\alpha$ -carboline. Since *Chem. Abstr.* does not index carbolines, but does carbazoles, 1,7-diazacarbazole would be a more appropriate aza name. The correct nomenclature based on the *Ring Index* system would be 4,8-dimethyl-9-phenyl-9H-pyrrolo[2,3-b:5,4-c']dipyridine.

7-Azatryptamine and 2-methyl-7-azatryptamine were refluxed with ethylisothiuronium bromide in water to give the corresponding guanidines.<sup>109b</sup>

#### 6. *Reactions of Methyl Substituents*

2,5-Dimethyl-4-azaindole (**164**) condensed readily with benzaldehyde to give a product assigned the styryl structure (**165**) in 80% yield.<sup>16</sup> However, condensation on the pyridyl-methyl group is more likely on mechanistic grounds. The phenethyl compound, allegedly **166**, obtained by catalytic reduction of **165** in 75% yield, gave on treatment with potassium permanganate in acetone the 4-oxide (**167**) (18%), which gave **166** on catalytic reduction. Attempts to prepare the azaindoles (**165** and **166**) by Madelung cyclization of 3-cinnamoyl- and 3-phenylpropionylamino-2,6-lutidines failed.<sup>16</sup>

As mentioned above, Yakhontov *et al.*<sup>103</sup> discuss the failure of the 4-methyl group in their series of 7-azaindoles to undergo condensation reactions with aldehydes over a wide temperature range and with various catalysts. It also fails to oxidize even with selenium dioxide at 170°.

The series of 7-, 4-, and 5-azaindolenine methiodides were prepared by Ficken and Kendall<sup>50, 51</sup> as intermediates for cyanine dyes. They were successful in preparing several of these, which may be represented by structures **168**,<sup>50</sup> **169**,<sup>51</sup> and **170**.<sup>111</sup>

### V. Physical Properties

The structures of the azaindoles were discussed in terms of  $\pi$ -electron density calculations in Section IV. Tautomeric forms of the azaindoles will be discussed under the various physical methods below.

#### A. IONIZATION CONSTANTS

The ionization constants of the four parent azaindoles<sup>14</sup> and three methyl-7-azaindoles<sup>23</sup> have been measured in water at 20°. These are listed in Table II together with a value assigned to 7-methyl-7*H*-7-azaindole,<sup>27</sup> which cannot be regarded with much confidence because of the method employed. Recently, Yakhontov *et al.*<sup>118a</sup> reported

<sup>118a</sup> L. N. Yakhontov, M. A. Portnov, M. Ya. Uritskaya, D. M. Krasnokutskaya, M. S. Sokolova, and M. V. Rubtsov, *Zh. Organ. Khim.* **3**, 580 (1967); *Chem. Abstr.* **67**, 21385 (1967).

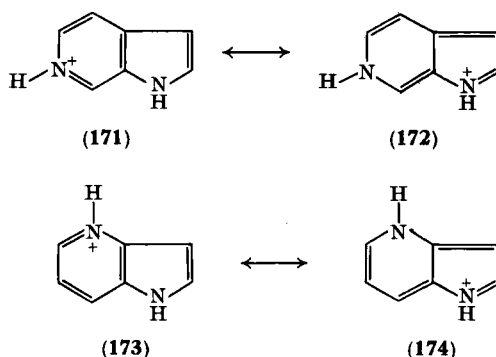
TABLE II  
IONIZATION CONSTANTS OF AZAINDOLES

Compound	pK <sub>a</sub> (basic) 20°	Method <sup>a</sup>	Reference
4-Azaindole	6.94	P	14
5-Azaindole	8.26	P	14
6-Azaindole	7.95	P	14
7-Azaindole	4.59	P	14
4-Methyl-	5.23	S	23
5-Methyl-	4.91	S	23
6-Methyl-	5.18	S	23
7-Methyl-	(8.9?)	H	27

<sup>a</sup> P = potentiometry, S = spectrophotometry, H = pH at half-neutralization. All were measured in water.

experimental and calculated pK<sub>a</sub> values for several 4-methyl-7-azaindoles and azaindoles.

The relative basic strengths of the parent azaindoles have been explained on the basis of resonance stabilization of the cations.<sup>14, 119</sup> In the case of protonated 5-azaindole (**101**) and 6-azaindole (**171**) resonance with the *para*-quinonoid forms **102** and **172** adds to greater stabilization than the *ortho*-quinonoid type necessary for the cation pairs **103**↔**104** and **173**↔**174**. Further, if the azaindoles are regarded as substituted aminopyridines, comparison with suitable model compounds permits a reasonable evaluation of the pK<sub>a</sub> values. A vinyl group is base-weakening (–I) in the 3-position of pyridine accounting



<sup>119</sup> A. Albert, *Phys. Methods Heterocyclic Chem.* **1**, 46 (1963).

for the lowered basic strength of 5-azaindole compared to 4-aminopyridine (9.17), but only partly so for 7-azaindole, whose  $pK_a$  is much lower than that of 2-aminopyridine (6.86). This has been explained by the nearness of the two nitrogen atoms, with the fractional positive charge of  $N_{(1)}$  possibly exerting a coulombic repulsion on an approaching proton.<sup>14</sup> In the 4-position a vinyl group is base-strengthening (+M) with 6-azaindole a stronger base than 3-aminopyridine (5.98). The increase in strength of 4-azaindole over 3-aminopyridine indicates that the resonance form (174) must contribute some stabilization, as 2-vinylpyridine ( $pK_a$  4.92) is a weaker base than pyridine (5.2), and the value predicted by the method of Clark and Perrin<sup>120</sup> for 3-amino-2-vinylpyridine is only ca. 5.6.

It was noted that the methyl-substituted 7-azaindoles show the same order of basic strength as 4-Me > 2-Me > 3-Me > unsubstituted pyridine, with a  $-\Delta pK_a$   $0.78 \pm 0.01$ , and 4-Me > 2-Me > 3-Me > 2-aminopyridine, with a  $-\Delta pK_a$   $2.27 \pm 0.04$ . Using these  $-\Delta pK_a$  values,  $pK_a$ 's were predicted for 6-chloro- (ca. 0.7) and 6-methoxy- (ca. 3.3) -4-methyl-7-azaindole (cf. Section IV,A).

It was noted above (Section IV,C,3) that the failure of 5-azaindole to undergo the Mannich reaction could be accounted for by its high basic strength. Difficulty might be expected also for 6-azaindole, and less so for 4-azaindole. The only attempt reported was successful with ethyl 5-methoxy-6-azaindole-3-carboxylate,<sup>66</sup> but the predicted  $pK_a$  for 5-methoxy-6-azaindole would be ca. 5.9, which may be lowered further by the electron-withdrawing ester group. It will be of interest to see how the parent azaindoles differ in these reactions.

The low  $pK_a$  of 8.9 for the 7-methyl compound compared to 1-methylpyrid-2-oneimine (12.2) cannot be assessed until a more accurate determination is made.

Ficken and Kendall<sup>50</sup> discuss the relative basicities of the pyridine and pyrrolenine nitrogen atoms in the azaindolenines (Scheme 7) based on Brooker deviation measurements from light-absorption data of their cyanine dyes. These indicate that  $N_{(7)}$  in the 7-azaindolenine (31) is considerably more basic than  $N_{(1)}$  in the sense that the 7-quaternary salt (117) displays less tendency to be stabilized by a  $N^{IV} \leftrightarrow N^{III}$  isomerization than does the 1-quaternary salt (120). They relate this to the formation of an unstable *o*-quinonoid resonance form. In the case of the 4-azaindolenine (32),<sup>51</sup> it was suggested that the pyridine  $N_{(4)}$  is expected to be more basic than  $N_{(1)}$ , although reaction<sup>120</sup> J. Clark and D. D. Perrin, *Quart. Rev. (London)* **18**, 295 (1964).



with methyl iodide gives only the 1-quaternized compound (122). This was explained by possible steric hindrance by the *gem*-dimethyl group,<sup>51</sup> or by an electronic influence.<sup>112</sup> The  $pK_a$ 's of these azaindoles would be of interest.

## B. SPECTRA

### 1. *Infrared Spectra*

Few complete infrared spectra have been reported for the azaindoles, although some partial band assignments have been made. In most cases, only the functional group frequencies of substituted azaindoles were reported.

For the purpose of this review, the infrared spectra of the four parent azaindoles were measured and the principal bands listed in Table III; those recorded in the literature are listed in Table IV. The frequencies are grouped into regions according to the scheme used by Katritzky and Ambler,<sup>121</sup> and the assignments can be considered only tentative until the spectra of more compounds are examined. For correlations with the spectra of pyrroles, indoles, and pyridines consult Katritzky and Ambler,<sup>121</sup> pp. 199, 211, and 274.

Although a detailed discussion of the spectra is beyond the scope of this review, a few comments seem in order.

The azaindole  $\nu$ NH absorbs quite consistently at  $3472\text{ cm}^{-1}$  in nonpolar solvent, and, because of this high frequency, hydrogen-bonding with the pyridine ring nitrogen does not seem to occur. The shift to lower frequency for solid samples is typical of indole  $\nu$ NH, and this band appeared at ca.  $3200\text{ cm}^{-1}$  in Nujol as in KBr.

The ring overtone region is similar for the 2,3-disubstituted pyridine pair 4- and 7-azaindole and the 3,4 pair, 5- and 6-azaindole. The ring-stretching patterns are characteristically different and show combinations of pyrrole and pyridine  $\nu$ C=C and  $\nu$ N=C modes, each compound giving six strong bands. The more basic pair, 5- and 6-azaindole, which are capable of *para*-quinonoid resonance, show the first strong band in this region at higher frequency.

The  $\beta$ CH modes are more variable and only the principal bands are listed. The last two bands, at ca.  $1150$  and  $1050\text{ cm}^{-1}$ , could be ring breathing modes.

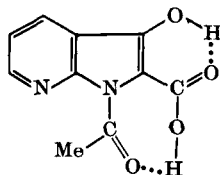
The  $\beta$ NH mode was assigned by virtue of its shift and broadening on going from solution to solid media. The groupings at  $917$  and  $814$

<sup>121</sup> A. R. Katritzky and A. P. Ambler, *Phys. Methods Heterocyclic Chem.* **2**, 161 (1963).

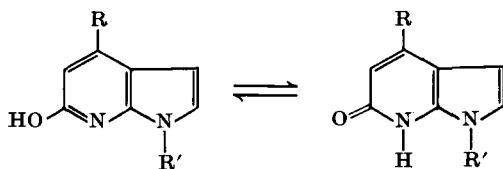
$\text{cm}^{-1}$  for 5-azaindole and 912 and  $832\text{ cm}^{-1}$  for 6-azaindole are consistent with  $\gamma\text{CH}$  of 3,4-disubstituted pyridines, and similarly the lower-frequency pairs  $803$  and  $725\text{ cm}^{-1}$  for 4-azaindole and  $799$  and  $724\text{ cm}^{-1}$  for 7-azaindole with 2,3-disubstituted pyridines. The most characteristic band for all four azaindoles in this region is at ca.  $900\text{ cm}^{-1}$ , and is probably  $\gamma\text{CH}$ . The  $\beta$  and  $\gamma$  ring modes fall in this region but were not assigned.

The substituted compounds listed in Table IV are consistent with these assignments.

Infrared spectral data available for those azaindole derivatives which are not completely aromatic, i.e., azaindolenines, azaindoxyls, and azaoxindoles, are listed in Table V.



(175)



(176)

(177)

The high-frequency  $\nu\text{C}=\text{O}$  is assigned to the acetoxy carbonyl in *O,N*-diacetyl-4-azaindoxyl; the lower band is *N*-acetyl. The splitting of these  $\nu\text{C}=\text{O}$  has been attributed by Su and Tsou<sup>122</sup> to intramolecular H-bonding of the carbonyl groups with the 2-hydrogen. The azaindoxylic acid derivative and its salt also show a multiplicity of  $\nu\text{C}=\text{O}$  bands. The presence of the bonded  $\nu\text{OH}$  peak at  $3150\text{ cm}^{-1}$  supports the enol indoxyl structure (84) for the acid, with expected intramolecular chelation of the 3-hydroxyl group with the carboxyl  $\text{C}=\text{O}$ . The very intense low-frequency band at  $1615\text{ cm}^{-1}$  is assigned to this carbonyl, so it appears the *N*-acetyl  $\text{C}=\text{O}$  is H-bonded by the carboxyl OH, giving rise to the doublet at higher frequency. This can be pictured as in 175. In addition, the  $\nu\text{C}=\text{O}$  in indoxyls with ring

TABLE III

INFRARED BANDS AND ASSIGNMENTS FOR THE AZAINDOLES (CM<sup>-1</sup>)<sup>a</sup>

Vibration type	4-Azaindole		5-Azaindole		6-Azaindole		7-Azaindole		
	KBr <sup>b</sup>	CHCl <sub>3</sub> <sup>c</sup>	KBr	CHCl <sub>3</sub>	KBr	CHCl <sub>3</sub>	KBr	CHCl <sub>3</sub>	C <sub>2</sub> Cl <sub>4</sub> <sup>d</sup>
$\nu$ NH	3200	3472	3200	3472	3200	3472	3200	3472	3472
$\nu$ CH	3125	-	3106	-	3125	-	3125	-	3145
	3077	-	3077	-	3067	-	3077	-	3077
	3030	-	3040	-	3030	-	3021	-	3012
	2985	-	2967	-	2959	-	2985	-	2933; 2890
Ring overtones	1942 w	1931 w	—	—	—	—	1923 w	1934 w	—
	1887 w	1887 w	1887 w	1894 w	1916 w	1901 w	1887 w	1894 w	—
	1842 w	1838 w	1859 w	1880 w	1786 w	1761 w	1848 w	1866 w	—
	1754 w	1757 w	1754 w	1764 w	1761 w	1748 w	1736 w	1748 w	—
	1733 w	1745 w	1739 w	1742 w	1742 w	1733 w	1704 w	1733 w	—
$\nu$ ring	—	—	1623 vs	1626 vs	1626	1623	1613	1613	1616
	1572 m	1572	1587	1587	—	—	1595 vs	1595 vs	1597 vs
	1506	1511	—	—	1515	1515	1511	1520	1511 m
	—	—	1477	1481	1475 vs	1475 vs	—	—	—
	1458	—	1453	1443	1435	1429	1433 vs	1431 vs	1433 vs
	1410 vs	1418 vs	1418	1418 vs	1418	1408	—	—	—
	1374	1370	1364 vs	1366	1372 vs	1370	1357 vs	1355	1355 vs
	1333	1325	—	—	—	—	1346 vs	1325	1333

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[SEC. V. B.1.]

$\beta$ CH	1294 vs 1263 m — 1133 m 1068	1287 vs - — 1131 m 1067 m	1311 vs 1279 1208 1170 1030 vs	1304 vs 1271 - 1183 1036 vs	1314 vs 1274 1227 1164 vs 1072	1304 1269 - 1174 1074 m	1289 vs 1261 m — 1133 m 1072 m	1290 vs - — 1122 m 1070 m	1292 vs - — 1129 m 1073 m
$\beta$ NH	1115	1099	1112	1070	1131	1104 m	1114	1096	1109
$\gamma$ CH, $\beta$ ring, and $\gamma$ ring	— 903 vs 892 vs 803 796 vs 780 vs 763 725	— 897 888 - - - - -	917 m 902 vs 889 m 814 803 vs 738 735 vs 730	- 903 vs 889 m - - — - -	912 900 vs 885 m 832 vs 778 770 740 vs —	- 894 883 m 822 vs - - - —	— 905 vs 889 — 799 768 vs 731 724	— 901 879 — - - - -	— - - — - - - -

<sup>a</sup> The spectral data were determined in the author's laboratory with a Perkin-Elmer Model 21 Spectrophotometer, which recorded linear in wavelength. The wavenumber values ( $\text{cm}^{-1}$ ) are calculated. The bands listed are of strong intensity unless designated as: w, weak; m, medium; vs, very strong. Those in italics are shoulders. A hyphen (-) indicates that the band was obscured by solvent absorption.

<sup>b</sup> Determined with a KBr disk made from 1.96 mg of compound and 200 mg of KBr.

<sup>c</sup> Determined as ca. 0.2 *M* chloroform solution in a 0.1-mm cell.

<sup>d</sup> Determined as ca. 0.2 *M* tetrachloroethylene solution in a 0.1-mm cell. 4-, 5-, and 6-azaindole were not soluble in this solvent.

TABLE IV  
INFRARED BANDS AND ASSIGNMENTS FOR SUBSTITUTED 7-AZAINDOLES (CM<sup>-1</sup>)

Vibration type	$\alpha$ -Me-7-azatryptamine <sup>a</sup> Nujol	6-Methoxy-4-methyl <sup>b</sup> Nujol      Dioxan	1-Phenyl-6-MeO-4-Me <sup>b</sup> Nujol      Dioxan	5-Hydroxy <sup>c</sup> KBr
$\nu$ NH	3190 <sup>d</sup>	3209      3314	-      -	3400 <sup>e</sup>
$\nu$ ring	1605	1615      1606	1597      1595	1590
	1579	—      —	—      —	—
	1533	1520      1525	1514      1517	—
	1490	1501      1501	1495      1499	1500

<sup>a</sup> W. R. N. Williamson, *J. Chem. Soc.*, 2833 (1962).

<sup>b</sup> L. N. Yakhontov, D. M. Krasnokutskaya, E. M. Peresleni, Yu. N. Sheinker, and M. V. Rubtsov, *Dokl. Akad. Nauk SSSR* **172**, 118 (1967); *Chem. Abstr.* **66**, 104506 (1967).

<sup>c</sup> M. M. Robison, B. L. Robison, and F. P. Butler, *J. Am. Chem. Soc.* **81**, 743 (1959).

<sup>d</sup> Pyrrole NH and NH<sub>2</sub>.

<sup>e</sup>  $\nu$ NH and OH.

TABLE V  
INFRARED BANDS AND ASSIGNMENTS FOR MISCELLANEOUS AZAINDOLES (CM<sup>-1</sup>)

Vibration type	Azaindolenines <sup>a</sup>			3,3-Me <sub>2</sub> -7-azaoxindole <sup>b</sup>	O,N-Ac <sub>2</sub> -4-azaindoxyl <sup>c</sup>	N-Ac-7-azaindoxylic acid <sup>c</sup>	
	4- <sup>d</sup>	5-	7-			Free acid	Sodium salt
$\nu$ NH,OH	—	—	—	3100 m	—	3150 b	3230
$\nu$ C=O	—	—	—	1720	1790;1765	1680	1665
	—	—	—	—	1720;1710	1645 b	1640
	—	—	—	—	—	1615 vs	1605 vs
$\nu$ ring	1605 m	1600 m	—	1610 <sup>e</sup>	1590	1580	1570
	1560 m	1560	1560	1442 w	1460	1520	1522 m
	1458 m	—	—	1430 m	1430	1460	—
	—	—	—	—	1400	—	1415
	—	—	—	—	1350	1360 m	1350
$\beta$ CH	1412 <sup>f</sup>	1410 m <sup>f</sup>	1400 <sup>f</sup>	1410 m <sup>f</sup>	1285	—	—
	—	—	—	—	1240	—	1230 m
	—	—	—	—	1190	1205 m	—
	—	—	—	—	1130 m	1100 w	1082 m
	—	—	—	—	1020 m	1065 m	1020 w
$\nu$ CO	—	—	—	—	1220	1320 b	1315
$\gamma$ CH,	—	942 m	—	—	940	960	—
$\beta$ ring,	813	934 m	—	—	815	—	865
and	786	877	875 m	—	790	—	780
$\gamma$ ring	—	842	807	781	775	770	770
	—	—	722 m	—	705	720 m	740;735

<sup>a</sup> G. E. Ficken and J. D. Kendall, *J. Chem. Soc.*, 3202 (1959).

<sup>b</sup> G. E. Ficken and J. D. Kendall, *J. Chem. Soc.*, 747 (1961).

<sup>c</sup> R. E. Willette, *J. Chem. Soc.*, 5874 (1965); unpublished results.

<sup>d</sup> Liquid film, all others in Nujol mulls. Symbols are the same as in Table III, with b=broad.

<sup>e</sup> Assigned to  $\beta$ NH.

<sup>f</sup> Assigned to methyl  $\beta$ CH.

carbonyls shows bands at higher frequencies.<sup>122, 123</sup> It is more difficult to explain the similar pattern in the sodium salt. The other assignments in Table IV are consistent with those reported,<sup>122</sup> except for the lack of a strong  $\nu\text{N}=\text{C}$  mode above  $1600\text{ cm}^{-1}$  for the azaindolenines.<sup>124</sup>

6-Hydroxy-7-azaindole (**176**,  $\text{R}=\text{R}'=\text{H}$ ) was shown to exist in the lactam form (**177**,  $\text{R}=\text{R}'=\text{H}$ ) with its infrared spectrum (KBr) showing  $\nu\text{C}=\text{O}$  at  $1650\text{ cm}^{-1}$ ,  $\nu\text{NH}$  at  $3400\text{ cm}^{-1}$ , and  $\beta\text{NH}$  at  $1610\text{ cm}^{-1}$ .<sup>69</sup> The 6-hydroxyazaindoline had  $\nu\text{C}=\text{O}$  at  $1640\text{ cm}^{-1}$ .

Yakhontov *et al.*<sup>83a</sup> discuss the tautomerism in 6-hydroxy-4-methyl-7-azaindoles (**176**  $\rightleftharpoons$  **177**,  $\text{R}=\text{Me}$ ), giving frequencies for  $\nu\text{C}=\text{O}$  (solid):  $1644\text{ cm}^{-1}$  ( $\text{R}'=\text{H}$ ),  $1659\text{ cm}^{-1}$  ( $\text{R}'=\text{Bu}$ ), and  $1642\text{ cm}^{-1}$  ( $\text{R}'=\text{Ph}$ ). In  $\text{CCl}_4$ , the last two compounds showed  $\nu\text{C}=\text{O}$  at  $1644$  and  $1642\text{ cm}^{-1}$  in addition to  $\nu\text{OH}$  at  $3580\text{ cm}^{-1}$ . The presence of appreciable lactim form (**176**) in nonpolar solvent was supported by ultraviolet spectral data (see below).

The functional group frequencies for substituted azaindoles will not be discussed here and the following references may be consulted: Robison *et al.*,<sup>68</sup> Yakhontov *et al.*,<sup>73, 77, 80, 81, 84, 85, 109</sup> and Blatter *et al.*<sup>115</sup>

## 2. Ultraviolet Spectra

The ultraviolet absorption spectra of azaindoles have been more thoroughly investigated and those recorded have been listed in Table VI. They are arranged roughly in the order of increasing substitution and complexity. The absorption maxima  $\lambda_{(\text{max})}$  have been organized into three bands, I, II, and III, which are all ascribable to  $\pi \rightarrow \pi^*$  transitions, and correspond to the three principal bands of indole. These have been related to the  $\beta$ ,  $p$ , and  $\alpha$  bands of pyridine and benzene by Mason,<sup>125</sup> and this reference should be consulted for a theoretical discussion of the transition origins and application to

<sup>122</sup> H. C. F. Su and K. C. Tsou, *J. Am. Chem. Soc.* **82**, 1187 (1960).

<sup>123</sup> See Katritzky and Ambler (ref. 121) p. 196.

<sup>124</sup> See Katritzky and Ambler (ref. 121) p. 187.

<sup>124a</sup> R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds" Wiley, New York, 1951.

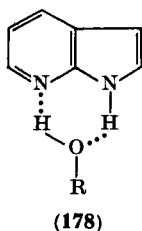
<sup>124b</sup> G. M. Badger and B. J. Christie, *J. Chem. Soc.* p. 3438 (1956).

<sup>124c</sup> R. E. Willette, unpublished results (1967).

<sup>125</sup> S. F. Mason, *Phys. Methods Heterocyclic Chem.* **2**, 1 (1963).

heterocyclic compounds.<sup>126</sup> No  $n \rightarrow \pi^*$  transitions have been demonstrated as yet for the azaindoles.

In general, most of the data reported are for spectra determined in hydroxylic solvents, which do not often show separation of bands II and III. The II or  $p$  band arises from a different transition than the  $\alpha$  band, and moves independently from it, showing greater sensitivity to conjugative effects and hydrogen-bonding.<sup>125</sup> When only one band at high wavelength is apparent, it is assigned in Table VI to band III assuming it to be a combination of  $p$  and  $\alpha$  bands.



A quick glance down Table VI shows that in most cases the  $p$  band lies under the envelope with the  $\alpha$  band. This appears most consistently with 7-azaindole, which can form an H-bonded complex as shown in 178. To confirm the presence of a  $p$  band, its spectrum was determined in heptane, and fine structure similar to that seen with indole in inert solvents is apparent. The same could be expected for 4-azaindole, but it, as well as the other two isomers, is not soluble in heptane or cyclohexane. It has been pointed out that the spectra in dichloromethane show little improvement over that in water.<sup>14</sup>

Adler and Albert,<sup>14</sup> as well as Mason,<sup>127</sup> have discussed the spectral data of the parent azaindoles in water as neutral molecules and cations. The large red shift of band III on going to the cations of 4- and 6-azaindole is characteristic of 3-aminopyridine. The red shift of 20  $m\mu$  for 5-azaindole is not in keeping with 4-aminopyridine (N: 268  $m\mu$ ,  $\log \epsilon$  3.72; C: 246  $m\mu$ ,  $\log \epsilon$  4.27<sup>128</sup>), but is for 3-vinylpyridine (N: 278  $m\mu$ ,  $\log \epsilon$  3.44; C: 287  $m\mu$ ,  $\log \epsilon$  3.52<sup>129</sup>) and for the *para*-quinonoid

<sup>126</sup> See also A. Albert, "Heterocyclic Chemistry," p. 296. Oxford Univ. Press, London and New York, 1959.

<sup>127</sup> See Mason (ref. 125) p. 65.

<sup>128</sup> S. F. Mason, *J. Chem. Soc.*, 219 (1960).

<sup>129</sup> M. L. Swain, A. Eisner, C. F. Woodward, and B. A. Brice, *J. Am. Chem. Soc.* **71**, 1341 (1949).



resonance form (102). 7-Azaindole is somewhat anomalous, not showing as large a red shift in the cation as 2-aminopyridine, indicating further that resonance stabilization to the *ortho*-quinonoid form (104) is not present to any large extent. However, in the acid spectrum of 7-azaindole reported by Robison and Robison,<sup>27</sup> a shoulder on the long-wavelength side of the band II–III envelope is apparent. That this is not indicative of *ortho*-quinonoid resonance is substantiated by the spectrum of 7-methyl-7*H*-7-azaindole, which shows a large red shift to 385 m $\mu$  in cyclohexane and alkaline aqueous solution. In acid solution, the spectrum reverts to that of 7-azaindole cation.

The spectrum of the 7-methyl-7*H* anhydro base (112), as well as the 7-benzyl and 7-*p*-nitrobenzyl compounds, was also studied by Saxena.<sup>110a</sup> In addition to showing that the maxima were solvent dependent, giving a blue shift in hydroxylic solvents, he suggests that the long wavelength absorption is due in part to the presence of the betaine form, where N<sub>(7)</sub> carries a positive charge and the unsubstituted N<sub>(1)</sub> a negative charge.

The only other *N*-methylated compound studied is apoharmine, i.e., 7-methyl-6-azaindole. The spectrum of its methiodide (107) in alcohol resembles that of 6-azaindole cation in water, whereas the spectrum in 0.01 *N* alcoholic potassium hydroxide shows a red shift to 385 m $\mu$ , being characteristic of the *para*-quinonoid form (109).

The methyl derivatives of 7-azaindole show effects similar to that seen in picolines with a blue shift for the 4-methyl isomer.

The other substituted azaindoles follow the expected patterns in their absorption spectra. 5-Hydroxy-7-azaindole gives a large red shift in its alkaline spectrum due to the strongly conjugative, electron-releasing anion. The spectrum of the 5-amino compound is similar. Halogen or methoxyl 6 substitution also gives a red shift. The 3-bromo compounds do not appear consistent, a red shift of band III and a blue shift of band II is reported for 3-bromo-7-azaindole, whereas the 4-methyl isomer shows a common envelope shifted slightly to the blue.

The nitro derivatives are interesting, showing strong absorption at long wavelengths, and giving spectra that resemble those of the 5-amino and 5-hydroxy compounds. The 6-methoxy-3-nitro compound has a band at 296 m $\mu$ , which corresponds in position to the band II–III envelope of the 6-methoxy compound, and one shifted to 380 m $\mu$ , due to the excited state involving the  $n \rightarrow \pi^*$  transitions of both groups.

The *N*-phenyl derivatives show blue shifts with band separation indicating a greater energy required for electron delocalization in the azaindole ring system. The strong long-wavelength band for the *p*-nitro compound is characteristic of substituted nitrobenzenes.

The typical red shifts on ring annelation are seen in 4,5-benzo-6-azaindole (45), which like 6-azaindole show a red shift of ca. 20  $m\mu$  in acid solution. The spectra of several substituted derivatives of this pyrroloquinoline are reported also, including the [2,3-*a*]naphthalene compound which has a max at 405  $m\mu$ .<sup>43</sup> The other  $\pi$ -conjugated derivatives all have bands at long wavelength, and are assigned the band positions indicated. The methylene malonate compound shows a four-band spectrum, with the  $\beta'$  band at 225  $m\mu$ .

The tautomeric 6-hydroxy-7-azaindole shows a shift to longer wavelength, which is characteristic of 2-hydroxypyridine as the neutral molecule or of 1-methyl-2-pyridone. The degree of tautomerization is solvent-dependent, and Yakhontov *et al.*<sup>83a</sup> have determined the lactam/lactim ( $176 \rightleftharpoons 177$ , R = Me) ratio from the position of the ultraviolet absorption maximum. The band at 298  $m\mu$  for 6-methoxy 176 (R = Me, R' = R) shifts to 327  $m\mu$  for the hydroxy 176 (R = Me, R' = H) in 75 % ethanol, where 99 % of the lactam is present. The ratio decreases to 0.32 in 15:85 ethanol-dioxan. The *N*-butyl isomers (176, R = Me, R' = Bu) favor the lactim form, and 50 % ethanol is required to obtain 99 % of lactam. The ratio is 0.11 in 25:75 ethanol-dioxan.

These workers<sup>83</sup> have used ultraviolet absorption to follow the course of dehydrogenation of 4-methyl-7-azaindoline. They also showed the spectra for the diazacarbazole derivatives (161 and 162), and these are like the spectra of the similarly substituted azaindoles.<sup>117</sup>

Adler<sup>130</sup> discusses the fluorescence properties of the azaindoles, which show in their excitation spectra bands similar to those in their absorption spectra but shifted to the red. A notable difference in the fluorescence intensity of the compounds was observed, with that of 4-azaindole being almost three times that of 7-azaindole, whereas the absorptivities in water are nearly the same. Similarly, 6-azaindole shows a higher intensity than 7-azaindole, although their emission peaks are at the same wavelength. This is even more exaggerated in the cations.

Table VII lists the ultraviolet absorption spectral data reported for azaindoles and azaindolenines. These are best considered as

<sup>130</sup> T. K. Adler, *Anal. Chem.* **34**, 685 (1962).

TABLE VI  
ULTRAVIOLET ABSORPTION SPECTRA OF AZAINDOLES

Compound <sup>a</sup>	Solvent <sup>b</sup>	$\lambda_{\max}$ m $\mu$ (log $\epsilon$ ) <sup>c</sup>			Reference
		Band I	Band II	Band III	
Indole	CH	220 (4.41)	262 (3.83)	280 (3.75)	124a
		—	266 (3.80)	288 (3.62)	124a
	A	[219 (4.5)]	[270 (3.8)]	[278 (3.8)]	124b
		—	—	[288 (3.7)]	124b
4-Azaindole, N	H <sub>2</sub> O	<i>d</i>	—	292 (3.92)	14
C	H <sub>3</sub> O <sup>+</sup>	<i>d</i>	284 (3.27)	327 (3.70)	14
5-Azaindole, N	H <sub>2</sub> O	<i>d</i>	265 (3.59)	273 (3.50)	14
C	H <sub>3</sub> O <sup>+</sup>	<i>d</i>	268 (3.46)	293 (3.29)	14
	A	216 (4.59)	—	265 (3.60)	18, 84
4-Me-5-azaindole	A	220 (4.90)	—	272 (4.05)	89
6-Azaindole, N	H <sub>2</sub> O	<i>d</i>	260 (3.59)	291 (3.68)	14
C	H <sub>3</sub> O <sup>+</sup>	<i>d</i>	261 (3.70)	319 (3.73)	14
	A	218 (4.78)	263 (3.92)	296 (4.02)	5
7-Me-6-azaindole	A	224 (4.54)	260 (3.86)	290 (4.00)	5
7-Azaindole, N	H <sub>2</sub> O	<i>d</i>	—	290 (3.91)	14
C	H <sub>3</sub> O <sup>+</sup>	<i>d</i>	—	293 (3.94)	14
	0.001 N HCl	[222 (4.25)]	[290 (3.9)]	[325 (2.9)]	27
	A	219 (4.13)	—	290 (3.91)	84
	Hep	<i>d</i>	280 (3.92)	294 (3.88)	124c
		—	288 (3.93)	—	124c

## C-Substituted 7-azaindoles

3-Me-	CH	225 (4.3)	—	290 (3.9)	27
4-Me-, N	H <sub>2</sub> O	<i>d</i>	—	285 (3.92)	23
C	H <sub>3</sub> O <sup>+</sup>	<i>d</i>	—	286 (3.95)	23
	A	220 (4.22)	—	288 (4.06)	79
5-Me-, N	H <sub>2</sub> O	<i>d</i>	—	293; 295 (3.89)	23
C	H <sub>3</sub> O <sup>+</sup>	<i>d</i>	—	295 (3.93)	23
6-Me-, N	H <sub>2</sub> O	<i>d</i>	—	293 (3.99)	23
C	H <sub>3</sub> O <sup>+</sup>	<i>d</i>	—	301 (4.06)	23
3,4-Me <sub>2</sub>	A	226 (4.15)	—	289 (3.80)	116
2,3-Butano	CH	228 (4.32)	—	292 (3.97)	41
3-Br	CH	222 (4.33)	287 (3.95)	295 (3.89)	107
4,6-Cl <sub>2</sub>	A	225 (4.40)	270 (3.66)	294 (3.74)	84
5-NH <sub>2</sub>	CH	<i>d</i>	280 (3.70)	326 (3.62)	69
5-HO	A	218 (4.23)	—	288 (3.85)	69
	0.05 N KOH, A	<i>d</i>	283 (3.88)	340 (3.85)	69
6-HO⇌O=	A	227 (4.17)	—	332 (3.93)	69
7-Azagramine	CH	[224 (4.25)]	—	[290 (3.9)]	22
7-Azatryptophan	H <sub>2</sub> O	[221 (4.35)]	—	[290 (3.9)]	22
C-Substituted 4-methyl-7-azaindoles					
6-Cl	A	224 (4.10)	—	292 (3.98)	79
6-I	A	228 (4.42)	—	290 (3.88)	79
6-MeO	A	222 (4.34)	—	298 (4.00)	79
3-Br	A	225 (4.38)	—	286 (3.89)	81
3-Br, 6-Cl	A	232 (4.38)	—	293 (3.95)	81
3-Br, 6-MeO	A	225 (4.24)	—	296 (3.92)	81
3-NO <sub>2</sub>	A	210 (4.27)	285 (4.01)	324 (3.80)	81
3-NO <sub>2</sub> , 6-Cl	A	218 (4.33)	283 (4.14)	324 (3.77)	81
3-NO <sub>2</sub> , 6-MeO	A	213 (4.32)	296 (3.88)	380 (4.04)	81

TABLE VI—*continued*

Compound <sup>a</sup>	Solvent <sup>b</sup>	$\lambda_{\max} \text{ m}\mu (\log \epsilon)^c$			Reference
		Band I	Band II	Band III	

N-Substituted azaindoles					
1-Me-6-aza	A	223 (4.58)	262 (3.72)	307 (4.06)	5
6,7-Me <sub>2</sub> -6-aza, C	A	<i>d</i>	[275 (3.9)]	[320 (3.9)]	110
N	A, OH <sup>-</sup>	<i>d</i>	[285 (3.7)]	[350 (3.6)]	110
1,6,7-Me <sub>3</sub> -6-aza, C	A	<i>d</i>	[275 (3.85)]	[330 (3.9)]	110
1-Me-7-aza	CH	[222 (4.2)]	[290 (3.9)]	[310 (3.25)]	27
7-Me-7H-7-aza	CH	245 (4.20)	309 (3.95)	385 (2.99)	27
	10 <sup>-4</sup> N NaOH	[232 (4.25)]	[302 (4.0)]	[350 (3.25)]	27
	10 <sup>-4</sup> N HCl	[223 (4.3)]	[290 (3.9)]	[330 (3.2)]	27
1,7-Me <sub>2</sub> -7-aza, C	H <sub>2</sub> O	227 (4.52)	—	296 (3.89)	27
7-CH <sub>2</sub> CO <sub>2</sub> H-7-aza, C	H <sub>2</sub> O	224 (4.30)	—	295 (3.95)	68
1,7-CH <sub>2</sub> CH <sub>2</sub> -7-aza, C	H <sub>2</sub> O	230 (4.20)	—	292 (3.94)	68
N-substituted 4-methyl-7-azaindoles					
1-Bu					
1-Bu, 6-MeO	A	222 (4.32)	—	296 (3.98)	83a
1-Ph	A	<i>d</i>	253 (4.34)	288 (3.88)	73
1- <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	A	<i>d</i>	253 (4.31)	282 (3.91)	74
1- <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	A	230 (4.18)	279 (4.02)	342 (4.17)	74
1-Ph, 6-MeO	A	<i>d</i>	256 (4.36)	292 (3.92)	83a
Azaindoles with $\pi$ -bonded substituents					
5-MeO-6-azaindole-2-CO <sub>2</sub> Et	A	<i>d</i>	278 (4.16)	344 (3.56)	66
		—	287 (4.23)	—	66
4,5-Benzo-6-aza	H <sub>2</sub> O	240 (4.47)	305 (4.03)	320 (3.91)	43
	H <sub>3</sub> O <sup>+</sup>	230 (4.37)	—	342 (4.03)	43

4-Me-7-azaindoles 3-CH=CNO <sub>2</sub>   H	A	224 (4.26)	286 (3.98)	387 (4.18)	116
6-Cl, 3-CH=CNO <sub>2</sub>   H	A	230 (4.25)	291 (4.07)	380 (4.04)	116
6-Cl, 3-CH=CNO <sub>2</sub>   H	A	232 (4.36)	292 (4.02)	373 (4.12)	116
6-Cl, 3-CH=CNO <sub>2</sub>   Me	A	234 (4.35)	291 (4.02)	370 (4.03)	116
1-Bu, 3-CH=CNO <sub>2</sub>   Et	A	246 (4.34)	285 (4.04)	395 (4.19)	77
1-Ph, 3-CH=CNO <sub>2</sub>   H	A	—	[290 (4.0)]	[390 (4.2)]	109
1-Ph, 3-CH=C(CO <sub>2</sub> Et) <sub>2</sub>   H	A	[255 (4.3)] [225 (4.25)] <sup>e</sup>	[280 (4.0)] —	[355 (4.25)] —	109 109
1-Ph, 3-CH=C(CO <sub>2</sub> H) <sub>2</sub>	A	—	[290 (4.0)]	[360 (4.35)]	109

<sup>a</sup> N = neutral molecule, C = cation, and are given only if the pH of the solution was reported.

<sup>b</sup> A = 95% ethanol, CH = cyclohexane, Hep = heptane.

<sup>c</sup> Shoulders or inflections are italicized. Values estimated from graphs are in brackets.

<sup>d</sup> Peaks at or below 220 mμ which were not measured or reported.

<sup>e</sup> See text.

TABLE VII  
ULTRAVIOLET ABSORPTION SPECTRA OF AZAINDOLINES AND AZINDOLENINES

Compound	Solvent <sup>a</sup>	$\lambda_{\max} m\mu (\log \epsilon)^b$			Reference
		Band I	Band II	Band III	
Indoline	A	—	—	290.5 (3.36)	130a
2-Methyl	A	239 (3.85)	—	290.5 (3.32)	130b
7-Azaindoline	CH	—	[243 (4.0)]	[308 (3.6)]	68
4-Me-7-azaindoline	A	—	248 (3.80)	306 (3.68)	79
6-Cl	A	—	256 (3.84)	312 (3.82)	79
6-MeO	A	—	247 (3.76)	306 (3.92)	79
1-Bu, 6-Cl	A	—	263 (3.97)	318 (3.73)	77
1-Ph	A	—	[280 (4.3)]	[323 (3.9)]	73
1- <i>p</i> -HOC <sub>6</sub> H <sub>4</sub>	A	234 (3.75)	284 (4.23)	320 (3.94)	74
1- <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	A	238 (3.78)	283 (4.24)	320 (3.99)	74
1- <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> , 6-Cl	A	236 (3.80)	289 (4.26)	334 (4.06)	74
1- <i>p</i> -Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	A	—	288 (4.26)	330 (4.06)	74
1- <i>p</i> -Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> , 6-Cl	A	242 (3.82)	297 (4.27)	340 (4.12)	74
1- <i>p</i> -N≡CC <sub>6</sub> H <sub>4</sub>	A	232 (3.94)	290 (4.14)	341 (4.60)	74
1- <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	A	302 (3.66)	314 (3.64)	396 (4.37)	74
		260 (4.08) <sup>c</sup>	—	—	74

Indolenines					
3,3-Me <sub>2</sub>	A	—	[245 (3.6)]	[262 (3.45)]	130c
2,3,3-Me <sub>3</sub>	A	—	[260 (3.75)]	[276 (3.6)]	130c
	A	—	257 (3.76)	?	50
	A, H <sup>+</sup>	226 (3.78)	—	274 (3.72)	50
1,2,3,3-Me <sub>4</sub> , I <sup>-</sup>	A	—	277 (3.97)	299 (3.49)	50
	A, OH <sup>-</sup>	—	278 (4.34)	308 (3.40)	50
1,3,3-Me <sub>3</sub> -2-methylene	A	—	[278 (4.20)]	[312 (3.35)]	130c
	MeOH	206 (4.31)	277.5 (4.16)	?	130d
	MeOH, HCl	229.5 (3.72)	236.5 (3.70)	274.5 (3.66)	130d
2,3,3-Me <sub>3</sub> -7-aza	A	—	245 (3.61)	280 (3.87)	50
	A, H <sup>+</sup>	240 (3.75)	282 (3.76)	300 (3.89)	50
1,2,3,3-Me <sub>4</sub> -7-aza, I <sup>-</sup>	A	248 (3.79)	274 (4.02)	317 (3.79)	50
	A, OH <sup>-</sup>	249 (3.87)	274 (4.02)	313 (3.72)	50
2,3,3,7-Me <sub>4</sub> -7-aza, I <sup>-</sup>	A	245 (3.66)	285 (3.76)	304 (3.86)	50
	A, OH <sup>-</sup>	293 (4.02)	345 (3.47)	362 (3.48)	50

<sup>a</sup> A = 95% ethanol, H<sup>+</sup> = acid, OH<sup>-</sup> = base, CH = cyclohexane.

<sup>b</sup> Shoulders and inflections are italicized. Values estimated from graphs are in brackets.

<sup>c</sup> See text.

<sup>130a</sup> T. Masamune, *J. Am. Chem. Soc.* **79**, 4418 (1957).

<sup>130b</sup> "Catalogue of Ultraviolet Spectra," Sadtler Spectrum No. 6720. Sadtler, Philadelphia, Pennsylvania, 1965.

<sup>130c</sup> P. Grammaticakis, *Compt. Rend.* **210**, 569 (1940).

<sup>130d</sup> "Catalogue of Ultraviolet Spectra," Sadtler Spectrum No. 6749. Sadtler, Philadelphia, Pennsylvania, 1965.



related to anilines, or, more appropriately, aminopyridines. Only data for 7-azaindolines have appeared, and these resemble indoline with band II shifting to the blue. *N* substitution causes a red shift, which is characteristic of anilines. The *p*-substituted 1-phenyl compounds show red shifts with inductive groups. The strongly conjugative *p*-nitro compound gives rise to a complex spectrum, with a fourth band appearing above 220 m $\mu$ .

The azaindolenines have been discussed by Ficken and Kendall,<sup>50</sup> who have pointed out that protonation, as well as methylation, of the 7 isomer (**31**, Scheme 7) occurs at N<sub>(7)</sub>, which can be seen from the similarity of the acid spectrum of the 2,3,3-trimethyl compound (**31**) and the alcoholic spectrum of the 7-methiodide (**117**). The behavior of the 7-methiodide in alkaline media is distinctly different from that of 1,2,3,3-tetramethyl indolenine iodide, which with alkali gives rise to the 2-methylene indoline, the spectrum of which was determined independently and is in agreement with this transformation, although the band appearing at ca. 300 m $\mu$  has not been reported in all cases. The bands indicated in Table VII for the MeOH/HCl spectrum of this compound should probably be stepped to the left. The large red shift shown by the 7-methiodide (**117**) is due to isomerization to the *ortho*-quinonoid compound (**118**). This does not take place in the hydrocarbons.

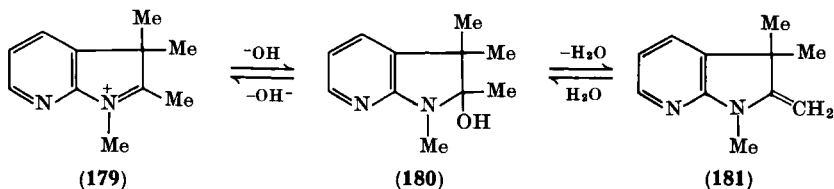
The behavior of the 1-methiodide (**179**) is more difficult to explain as its spectrum in alcohol is nearly identical to that in alkaline solution, and these both show the same pattern as the 2-methylene indoline, i.e., with an intensified band II and a band III shifted to the red as compared to its methiodide. It seems possible that these compounds exist as the carbinolamine, or pseudobase, in hydroxylic solvents and are in tautomeric equilibrium (**179** $\rightleftharpoons$ **181**). The direction of this equilibrium has been attributed by Beke<sup>131</sup> to the basicity of the nitrogen, as well as other factors. Bláha and Červinka<sup>132</sup> discuss the importance of steric and polar structural factors, citing examples of stable pyrrolidine pseudobases. Indeed, Ficken and Kendall<sup>51</sup> isolated the 4-azaindoline pseudobase (**123**), characterizing it by analysis and infrared spectral evidence. They similarly characterized the 2-methylene base (**121**), and it is unfortunate that their ultra-violet spectra were not determined. The 2-methylene-7-azaindoline

<sup>131</sup> D. Beke, *Advan. Heterocyclic Chem.* **1**, 170 (1963).

<sup>132</sup> K. Bláha and O. Červinka, *Advan. Heterocyclic Chem.* **6**, 157 (1966).

(181) was not isolated and its spectrum in a nonpolar solvent may prove revealing.

Reference spectra for these compounds involving anilines show differences between aniline anils and *N*-vinyl anilines that are characterized by the difference in the spectra of 2,3,3-trimethylindolenine and 1,3,3-trimethyl-2-methyleneindoline.<sup>133</sup> No suitable carbinolamine spectrum could be found, and the  $\lambda_{\max}$  values given for this



chromophore by Scott<sup>134</sup> are not applicable as it exists in a highly substituted, polyring system. Further evidence as to the nature of compound 179 in various solvents would be of interest.

The tautomerism of 6-hydroxy- and 6-amino-7-azaindoles was studied by Yakhontov *et al.*<sup>80</sup> The former, in contrast to other analogous *N*-heteroaromatic compounds, is not completely shifted to the lactam; whereas the latter, and its acyl derivatives, exist almost completely in the amino form. They suggest this is due to delocalization of the electrons between the nitrogen atoms of the two rings.

### 3. Nuclear Magnetic Resonance

The NMR spectra of azaindoles have received little attention. Frydman *et al.*<sup>66</sup> reported the spectrum of ethyl 5-methoxy-6-azaindole-2-carboxylate to show peaks for 3-H, 4-H, and 7-H in  $\text{CDCl}_3$  at 7.1, 7.2, and 8.7  $\delta$ , respectively. The 3-dimethylaminomethyl derivative, as the dihydrochloride in  $\text{D}_2\text{O}$ , showed 7-H at 8.2  $\delta$ .

Yakhontov *et al.*<sup>116</sup> reported NMR spectral data for three 7-azaindole derivatives in  $\text{CCl}_4$ . 4-Methyl-7-azaindole showed the  $\text{CH}_3$  at 7.47  $\tau$ , and the 2-H, 3-H, 5-H, and 6-H peaks at 2.70, 3.62, 3.21, and 1.88  $\tau$ , respectively. The 6-chloro isomer gave peaks for the

<sup>133</sup> P. Grammaticakis, *Bull. Soc. Chim. France*, 134 (1949).

<sup>134</sup> A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," p. 176. Macmillan, New York, 1964.

TABLE VIII  
NMR PARAMETERS OF AZAINDOLES<sup>a</sup>

Compound	Solvent <sup>b</sup>	Chemical shifts ( $\delta$ ) <sup>c</sup>						Coupling constants (c/sec)								
		2-H	3-H	4-H	5-H	6-H	7-H	$J_{12}$	$J_{13}$	$J_{23}$	$J_{45}$	$J_{46}$	$J_{47}$	$J_{56}$	$J_{57}$	$J_{67}$
4-Azaindole	CDCl <sub>3</sub>	7.56	6.78	—	8.54	7.14	7.76	2.5	<1	3.5	—	—	—	4.6	1.5	8.0
	DCl/D <sub>2</sub> O	7.91	6.62	—	8.34	7.46	8.26	—	1.0	3.5	—	—	—	6.0	1.0	8.0
5-Azaindole	CDCl <sub>3</sub>	7.38	6.70	9.20	—	8.34	7.39	1.0	1.0	3.2	—	—	1.0	—	—	5.6
	DCl/D <sub>2</sub> O	7.77	6.94	8.90	—	8.21	7.78	1.0	1.0	3.5	—	1.0	0.75	—	—	7.0
6-Azaindole	CDCl <sub>3</sub>	7.49	6.60	7.63	8.30	—	8.88	1.0	1.0	3.0	5.5	—	1.0	—	—	—
	DCl/D <sub>2</sub> O	8.09	6.84	7.98	8.18	—	8.79	1.0	1.0	3.0	4.5	—	1.0	—	—	—
7-Azaindole	CDCl <sub>3</sub>	7.42	6.52	8.00	7.10	8.39	—	—	—	3.0	7.5	2.0	—	4.5	—	—
	DCl/D <sub>2</sub> O	7.58	6.71	8.47	7.44	8.26	—	—	—	3.5	7.5	1.75	—	6.0	—	—
4-Methyl-	CDCl <sub>3</sub>	7.39	6.54	2.58	6.92	8.28	—	—	—	3.5	—	—	—	5.0	—	—
	DCl/D <sub>2</sub> O	7.26	6.53	2.50	7.11	7.99	—	—	—	4.0	—	—	—	6.5	—	—
5-Methyl-	CDCl <sub>3</sub>	7.38	6.39	7.79	2.44	8.24	—	—	—	3.5	—	2.0	—	—	—	—
	DCl/D <sub>2</sub> O	7.53	6.56	7.97	2.42	8.12	—	—	—	3.5	—	ca. 2	—	—	—	—
6-Methyl-	CDCl <sub>3</sub>	7.34	6.48	7.86	6.95	2.70	—	—	—	3.5	8.0	—	—	—	—	—
	DCl/D <sub>2</sub> O	7.45	6.61	8.22	7.15	2.67	—	—	—	3.5	8.0	—	—	—	—	—

<sup>a</sup> Determined in these laboratories with a Varian A-60 Spectrometer at 40°, with ca. 10% solutions.

<sup>b</sup> CDCl<sub>3</sub> = deuteriochloroform, DCl/D<sub>2</sub>O = 1 gm deuterium chloride in 10 gm deuterium oxide.

<sup>c</sup> The chemical shifts ( $\delta$ , TMS = 0) for CDCl<sub>3</sub> solutions are relative to internal TMS, and, for DCl/D<sub>2</sub>O solutions, relative to external TMS.

R. E. WILLETTTE

[Sec. V. B.3.]

$\text{CH}_3$ , 2-H, and 3-H at identical positions. The 5-H was not apparent in the spectrum. Similarly, the spectrum of 3,4-dimethyl-7-azaindole showed two  $\text{CH}_3$  peaks at 7.60 and 7.40  $\tau$ , but no ring proton peaks were distinguishable because of low solubility.

Crooks and Robinson<sup>49a</sup> reported the spectrum of 2,3-dimethyl-5-azaindole in hexadeuterodimethyl sulfoxide to show peaks at 7.73 $\tau$  (3- $\text{CH}_3$ ), 7.68 $\tau$  (2- $\text{CH}_3$ ), doublets centered at 2.76 (7-H) and 1.89 $\tau$  (6-H,  $J=5.5$  c/sec), and a broad singlet at 1.32 $\tau$  (4-H). The NH proton appeared as a broad singlet at -1.13 $\tau$ .

TABLE IX  
EFFECTS ON *N*-DEUTERONATION ON THE CHEMICAL SHIFTS OF  
AZAINDOLES

Compound	Chemical shifts (ppm) relative to the 3-hydrogen of cation minus that of neutral molecule <sup>a</sup>				
	2-H	4-H	5-H	6-H	7-H
4-Azaindole	0.51	—	-0.04	0.48	0.66
5-Azaindole	0.15	-0.54	—	-0.37	0.15
6-Azaindole	0.26	0.11	-0.36	—	-0.33
7-Azaindole	-0.03	0.28	0.15	-0.32	—
4-Methyl-	-0.12	0.07 <sup>b</sup>	0.20	-0.28	—
5-Methyl-	-0.02	0.01	0.19 <sup>b</sup>	0.11	—
6-Methyl-	-0.02	0.23	0.07	0.16 <sup>b</sup>	—

<sup>a</sup>  $[\text{X-H}\delta - 3\text{-H}\delta(\text{DCl}/\text{D}_2\text{O})] - [\text{X-H}\delta - 3\text{-H}\delta(\text{CDCl}_3)]$ .

<sup>b</sup>  $\text{CH}_3$ .

For the purpose of this review, the NMR spectra of the four parent azaindoles and the three methyl-7-azaindoles prepared earlier by us<sup>23</sup> were determined in  $\text{CDCl}_3$  and in  $\text{DCl}/\text{D}_2\text{O}$  solution. The chemical shifts ( $\delta$ , ppm) and coupling constants (c/sec) for these compounds are listed in Table VIII.

Direct correlation between the two solvents is not applicable, as shifts due to solvent interactions are expected. It was found useful to compare the chemical shifts of each proton relative to the 3-hydrogen for both solvents, and these are compiled in Table IX. The 3-hydrogen was chosen as a reference point as it appears farthest up field, and is subject to the least degree of shifting, being at ca.  $6.6 \pm 0.3 \delta$  in all fourteen spectra. It can be seen from Table IX that *N*-deuteronation causes a shift to low field relative to the 3-hydrogen for all  $\beta$ - and

$\gamma$ -hydrogens in the pyridine ring, and a shift to high field (negative values) for all  $\alpha$ -hydrogens, with the exception of 6-H in 5-methyl-7-azaindole. The 2-H in all four 7-azaindoles also shows a shift to high field, whereas the 2-H of 4- and 6-azaindoles shows the greatest low field shift.

The chemical shifts for each proton is in keeping with its position relative to the pyridine nitrogen, with the order towards high field being  $\alpha$ -,  $\gamma$ -,  $\beta$ -hydrogens. This is the same as in pyridine. The coupling constants are also in line with those observed in pyridine derivatives, with the order of increasing  $J$  values relative to the pyridine nitrogen being  $J_{25} < J_{24} < J_{23} < J_{34}$ . The only case of apparent 2,6-coupling is in the DCl/D<sub>2</sub>O spectrum of 5-azaindole where the 4- and 6-protons are split (1 c/sec) in addition to their coupling with the 7-H. The 6-H appears as a pair of doublets and the 4-H a doubly split singlet.

Unlike indole, the 2- and 3-protons couple with a large enough splitting (3 to 4 c/sec) that, when coupling with the NH proton occurs, it gives rise to distinct pairs for each proton. One exception is noted in the CDCl<sub>3</sub> spectrum of 4-azaindole, where the 2-H appears as a partially resolved, broad doublet. Greater resolution shows it split (2.5 c/sec), presumably by the NH proton. The 3-H also appears as a broad doublet. In DCl/D<sub>2</sub>O, these peaks appear as a sharp doublet and a pair of doublets, respectively.

Interestingly, no splitting of the 2-H and 3-H by the NH proton is apparent in the spectrum of the 7-azaindoles. The NH proton was found in the CDCl<sub>3</sub> spectra as a low, broad hump at ca. 12.1 to 12.3  $\delta$ , corresponding to that seen for indole at ca. 10  $\delta$ .

Other work on the NMR of these compounds is in progress, and a detailed discussion of this data will be the subject of a future publication.

### C. MISCELLANEOUS

Some gas chromatography data for 7-azaindole has been reported,<sup>91</sup> and served as a means of identifying its presence in the pyrolysis products of nicotine.

Snyder<sup>135</sup> studied the adsorption energy of 7-azaindole by means of linear elution adsorption chromatograph. It showed an adsorption energy nearly identical to that of 2-aminopyridine and  $\alpha$ -carboline, and appeared characteristic of the  $\text{—N=C—NH}$  group.

<sup>135</sup> L. R. Snyder, *J. Chromatog.* **17**, 73 (1965).

Adler and Albert<sup>136</sup> have reported the partition coefficients for the parent azaindoles. The oleyl alcohol–water solubility ratio for the neutral molecules at 25° are 53.2, 36.8, 17.3, and 13.1 for 7-, 6-, 5-, and 4-azaindole, respectively. For comparison, indole, which is not basic, is more lipid-soluble, with a ratio of 85.7. The order for the azaindoles does not parallel their basic strength. The per cent of ionization at pH 7.4 was also calculated and for the above order is 0.15, 78.02, 87.87, and 27.75 %, respectively. The effects of these properties on the biological activity of the azaindoles is discussed also (see below).

## VI. Biological Properties

The first attempt to prepare an azaindole as an azalog of biologically active compounds appears to have been made by Bernstein *et al.*<sup>88</sup> They synthesized 6-amino-2,3-diphenyl-7-azaindole and tested it for antimalarial activity against *Plasmodium lophurae*. It showed little activity.

Protiva *et al.*<sup>17</sup> prepared a series of 1-dialkylaminoalkyl derivatives of 5-methyl-2-phenyl-4-azaindole as possible antihistaminics, but found them to be inactive.

As pointed out in the introduction, interest in the azaindoles was stimulated by their potential usefulness as azalogs of indole derivatives. Robison and Robison<sup>107</sup> prepared 7-azaindoleacetic acid, 7-azaindolepropionic acid, 7-azatryptophan, and 7-azatryptamine for this purpose, and reports on their biological activity have appeared for all but the last compound.

7-Azatryptophan has been studied to the greatest extent, and has shown significant antimetabolic properties. With the protozoan organism *Tetrahymena pyriformis*, it was shown to cause competitive inhibition of tryptophan incorporation.<sup>137</sup> In *E. coli* mutants and certain bacteriophage, it was found to incorporate into the protein structure producing inactive enzymes.<sup>138, 139</sup> It did not appear to replace tryptophan, however, but its incorporation caused major imperfection in the enzyme structure. 7-Azaindole, as well as indole, prevented protein synthesis in these organisms, which were tryptophan-requiring mutants.<sup>139</sup> With a mutant of *Neurospora*

<sup>136</sup> T. K. Adler and A. Albert, *J. Med. Chem.* **6**, 480 (1963).

<sup>137</sup> G. W. Kidder and V. C. Dewey, *Biochim. Biophys. Acta* **17**, 288 (1955).

<sup>138</sup> A. B. Pardee, V. G. Shore, and L. S. Prestidge, *Biochim. Biophys. Acta* **21** 406 (1956).

<sup>139</sup> A. B. Pardee and L. S. Prestidge, *Biochim. Biophys. Acta* **27**, 330 (1958).

*crassa* which utilizes both indole and tryptophan, 7-azaindole competitively inhibited indole utilization, but 7-azatryptophan had no effect on tryptophan incorporation.<sup>140</sup> More recently, results in animals show similar properties, with 7-azatryptophan being incorporated into rat plasma proteins, which lose their biological activity, and in turn cause a rapid loss in weight in the animal.<sup>141</sup>

The azaisatogens synthesized by Hooper *et al.*<sup>20a</sup> were effective against gram-positive organisms. Also, the 2-pyridyl-6-azaindoles showed a broader spectrum of antibacterial activity and were generally more effective than the analogous indoles.

Results with plants show the azalog of indoleacetic acid to be a powerful auxin in *Pisum* (pea) and *Avena* (oat) growth.<sup>142</sup> This and the propionic acid isomer also proved to be effective with *Parthenocissus tricuspidata* (Boston ivy) tissue.<sup>143</sup> 7-Azatryptophan was found to inhibit  $\alpha$ -amylase synthesis in barley endosperm tissue.<sup>143a</sup>

The thiosemicarbazone of 7-azaisatin lacked antiviral activity; isatin and pyridinecarboxaldehyde derivatives are active.<sup>144</sup>

The biological properties of the azaindoles in animals have been studied by Adler and Albert<sup>136</sup>; 4-, 5-, and 6-azaindole resemble indole *in vivo*, producing convulsions, although at much lower doses. 7-Azaindole has an opposite effect causing paralysis and respiratory depression. It also shows a delayed toxic effect, resulting in death of the animal. The methyl-7-azaindoles have similar activity, but the 6-methyl isomer was much less potent and did not show the delayed toxicity. At low doses, the 5-methyl isomer produced hyperexcitability. On isolated smooth muscle preparations, 4- and 7-azaindole caused relaxation, and antagonized the effects of 5-hydroxytryptamine. The 5 and 6 isomers acted like it in producing muscle contraction. Little correlation between these biological properties and the physical properties of the azaindoles was discernible.

Injection of 5-azaindole directly into the lateral geniculate nucleus

<sup>140</sup> E. R. B. Shanmugasundaram and P. S. Sharma, *Current Sci. (India)* **26**, 13 (1957).

<sup>141</sup> A. Berecz and C. Godin, *Can. J. Biochem. Physiol.* **40**, 153 (1962).

<sup>142</sup> K. V. Thimann, *Plant Physiol.* **33**, 311 (1958).

<sup>143</sup> H. H. Robson, H. T. Yost, Jr., and M. M. Robison, *Plant Physiol.* **36**, 621 (1961).

<sup>143a</sup> J. E. Varner, G. R. Chandra, and M. J. Chrispeels, *J. Cellular Comp. Physiol.* **66** [2], 55 (1965).

<sup>144</sup> P. W. Sadler, *J. Org. Chem.* **26**, 1315 (1961).

of the cat showed it to have no activity, whereas several indole derivatives produce marked effects.<sup>145</sup>

The azaindolyalkanoamidoximes, amidines, and guanidines were claimed to be hypotensive.<sup>109b</sup> The amidoximes also showed sedative and psychomotorial activity stimulating properties. 7-Azaindole-3-acetamidoxime has been studied more extensively, and found to produce a gradual, sustained lowering of blood pressure in hypertensive dogs.<sup>146</sup> This activity appeared to be due to catecholamine depletion of the heart.

A patent<sup>70</sup> describing the synthesis of azalogs of the drug indomethacin claims the 7-azaindole derivative to have anti-inflammatory, analgesic, and antipyretic properties.

Pharmacological data for several of the other azaindole derivatives of biological interest have not appeared as yet. Those of particular interest are 12-azadeserpidine,<sup>113</sup> 5-azatryptamine,<sup>58</sup> the several 4-methyl-7-azatryptamines,<sup>116</sup> and the azaharman analogs.<sup>117</sup>

#### ACKNOWLEDGMENT

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<sup>145</sup> D. R. Curtis and R. Davis, *Brit. J. Pharmacol.* **18**, 236 (1962).

<sup>146</sup> M. R. Bell, J. O. Hoppe, H. E. Lape, D. Wood, A. Arnold, and W. H. Selberis, *Experientia* **23**, 298 (1967).



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# The 1,2,5-Thiadiazoles

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## I. Introduction

### A. HISTORICAL

Of the four possible thiadiazoles (1-4), derivatives of **1**, **2**, and **3** were known for many years and the parent compounds themselves have been described. It was not until 1957 that mononuclear derivatives of 1,2,5-thiadiazole were reported although bicyclic and polycyclic systems involving the 1,2,5-thiadiazole system have been

known since 1889<sup>1</sup> and studied by a number of investigators. Thus, the history of the 1,2,5-thiadiazoles closely parallels that of the isothiazoles.<sup>2</sup> Since the first synthesis of **4** and its derivatives, much research concerned with the chemistry of this interesting heterocycle has been reported and many new and efficient syntheses have been developed.



(1,2,3-)

(1)



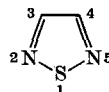
(1,2,4-)

(2)



(1,3,4)

(3)



(1,2,5-)

(4)

The unusual N—S—N bond system in 1,2,5-thiadiazoles poses interesting theoretical questions. Some insight into the structure and properties of 1,2,5-thiadiazoles was gained through studies of electron and X-ray diffraction, the microwave spectrum, and the Raman and infrared spectra of **4** and its derivatives. The iso- $\pi$ -electronic relationship between the 1,2,5-thiadiazoles and the pyrazines was examined in detail and a comparative study of the four isomeric thiadiazoles using the MO method in the LCAO approximation for small heterocyclic molecules was reported.

The purpose of this chapter is to review the organic and physical chemistry of monocyclic 1,2,5-thiadiazoles up to the early part of 1967. Reference is made to the 2,1,3-benzothiadiazoles and related compounds only as they contribute to the chemistry of the basic ring system. The four isomeric thiadiazoles, including their benzo derivatives, were previously reviewed by Bambas,<sup>3</sup> Grignard,<sup>4</sup> and Sherman<sup>5</sup> and the chemistry of 1,2,4-thiadiazoles was reviewed by Kurzer.<sup>6</sup>

<sup>1</sup> O. Hinsberg, *Chem. Ber.* **22**, 2895 (1889).

<sup>2</sup> R. Slack and K. R. H. Wooldridge, *Adv. Heterocyclic Chem.* **4**, 107-120 (1965).

<sup>3</sup> L. L. Bambas, "The Chemistry of Heterocyclic Compounds," p. 205. Wiley (Interscience), New York, 1952.

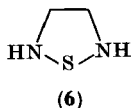
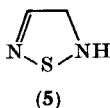
<sup>4</sup> V. Grignard, G. Dupont, and R. Locquin, "Traité de chimie organique," Vol. XXI, p. 1039. Masson, Paris, 1953.

<sup>5</sup> W. R. Sherman, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, Chapter 7, p. 579. Wiley, New York, 1961.

<sup>6</sup> F. Kurzer, *Advan. Heterocyclic Chem.* **5**, 119-204 (1965).

## B. NOMENCLATURE

The 1,2,5-thiadiazole nucleus is numbered as in 4. The hydrogenated forms (5 and 6) are referred to as 1,2,5-thiadiazoline and 1,2,5-thiadiazolidine according to the Patterson Ring Index. The benzo derivatives are numbered as in 7 and are named 2,1,3-benzothiadiazole though much of the early literature makes use of the name piazthiole. In an apparent confusion with the numbering system of the 2,1,3-benzothiadiazole some modern authors have used the name 2,1,3-thiadiazole in reference to the monocyclic derivatives.



## II. Synthesis of 1,2,5-Thiadiazoles

## A. BY DEGRADATION OF BICYCLIC 1,2,5-THIA DIAZOLE DERIVATIVES

## 1. Oxidation of 2,1,3-Benzothiadiazoles

The oxidation of 2,1,3-benzothiadiazole (7) was first examined in 1889 by Hinsberg<sup>1</sup> who found that the action of potassium permanganate in acidic medium led to total destruction of the compound while chromic acid was without effect. In 1957–1958 the successful oxidation of 2,1,3-benzothiadiazoles to 1,2,5-thiadiazole-3,4-dicarboxylic acid (8) was reported independently by two research groups.<sup>7–12</sup> This

<sup>7</sup> A. M. Khaletskii, V. G. Pesin, and T. Chow, *Dokl. Akad. Nauk SSSR* **114**, 811 (1957); *Chem. Abstr.* **52**, 4605 (1958) [see *Proc. Acad. Sci. USSR, Chem. Sect. (English Transl.)* **114**, 593 (1957)]. V. G. Pesin, A. M. Khaletskii, and T. Chow, *Zh. Obshch. Khim.* **28**, 2089 (1958); *Chem. Abstr.* **53**, 2214 (1959) [see *J. Gen. Chem. USSR (English Transl.)* **28**, 2126 (1958)].

<sup>8</sup> L. M. Weinstock, Ph.D. Dissertation, Indiana University (1958); *Dissertation Abstr.* **19**, 3136 (1959).

<sup>9</sup> M. Carmack, L. M. Weinstock, and D. Shew, *Abstr. 136th Nat. Meeting Am. Chem. Soc., Atlantic City* 1959 p. 37P.

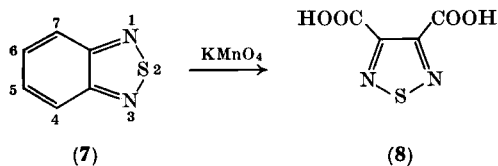
<sup>10</sup> M. Carmack, D. Shew, and L. M. Weinstock, U.S. Patent 2,980,687 (1961); *Chem. Abstr.* **55**, 21147 (1961).

<sup>11</sup> V. G. Pesin, A. M. Khaletskii, and E. K. D'yachenko, *Zh. Obshch. Khim.* **32**, 3505 (1962); *Chem. Abstr.* **58**, 12532 (1963) [see *J. Gen. Chem. USSR (English Transl.)* **32**, 3440 (1962)].

<sup>12</sup> V. G. Pesin, V. A. Sergeev, and A. M. Khaletskii, *Zh. Obshch. Khim.* **34**, 3753 (1964); *Chem. Abstr.* **62**, 9122 (1965) [see *J. Gen. Chem. USSR (English Transl.)* **34**, 3803 (1964)].

marked the first synthesis of mononuclear 1,2,5-thiadiazole although the method employed was long known in the synthesis of other heterocyclic systems, i.e., pyrazine-2,3-dicarboxylic acid by the oxidative degradation of quinoxaline.<sup>13</sup>

2,1,3-Benzothiadiazole is oxidized by ozone,<sup>7</sup> potassium permanganate,<sup>8-10</sup> and chromic acid<sup>12</sup> which all lead to the dicarboxylic acid (8). In the ozonolysis the intermediate crystalline ozonide is decomposed to 1,2,5-thiadiazole-3,4-dicarboxaldehyde (isolated as the semicarbazone) as well as 8. Permanganate oxidation has been applied to a number of derivatives of 7, among them being the 5-methyl,<sup>14</sup> 4-nitro,<sup>8-10</sup> and 4,7-dichloro<sup>11</sup> derivatives. In some cases, particularly in the permanganate oxidation of 4-nitro-2,1,3-benzothiadiazole, the yield of 8 is much higher than in the oxidation of the unsubstituted compound (7).



The action of peracids on 7 and many substitution derivatives always leads to cleavage of the thiadiazole ring with formation of ammonium sulfate.<sup>7, 11</sup>

Some by-products of the permanganate oxidation of 7 have been isolated and characterized. Both Shew<sup>15</sup> and Pesin *et al.*<sup>11</sup> detected the glycol (9) among the oxidation products, the latter workers oxidizing 9 to the aldehydic acid (10) with periodic acid. A second by-product which forms in much higher yield, and is in fact the major product when the permanganate oxidation of 7 is carried out at 100°, was at first assigned the structure 11 on the basis of its infrared spectrum,  $pK_a$ , and microanalysis.<sup>15</sup> A monopotassium salt isolated by Pesin *et al.*<sup>11</sup> was assigned the same skeletal structure. Wen<sup>16</sup> later showed that the dipotassium salt was a derivative of *N*-sulfamoyloxa-

<sup>13</sup> S. Gabriel and A. Sonn, *Chem. Ber.* **40**, 4850 (1907).

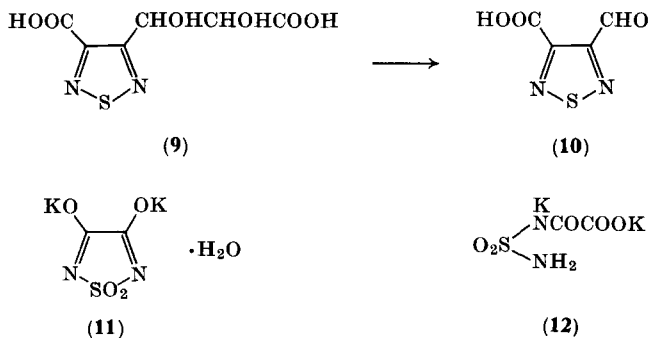
<sup>14</sup> I. Sekikawa, *Bull. Chem. Soc. Japan* **33**, 1229 (1960); *Chem. Abstr.* **55**, 7425 (1961).

<sup>15</sup> D. Shew, Ph.D. Dissertation, Indiana University (1959); *Dissertation Abstr.* **20**, 1593 (1959).

<sup>16</sup> R. Y. Wen, Ph.D. Dissertation, Indiana University (1962); *Dissertation Abstr.* **23**, 4121 (1963).

mic acid (**12**) and synthesized the compound by an independent route from sulfamide and methyl oxalate. Compound **12** was also employed in the synthesis of 1,2,5-thiadiazole-1,1-dioxides and is discussed further in Section II,D.

In earlier accounts of the permanganate oxidation of **7** by Khaletskii *et al.*<sup>7</sup> the principal product was reported as 1,2,5-thiadiazole-3,4-dicarboxylic acid-1,1-dioxide. This structure was later corrected to



the monopotassium salt of 1,2,5-thiadiazole-3,4-dicarboxylic acid.<sup>11</sup> However, in some later papers by other workers, the erroneous 1,1-dioxide structure is cited in discussion of the earlier work.

## 2. Hydrolytic Cleavage of [1,2,5]Thiadiazolo[3,4-*d*]pyrimidines



The formation of 3-amino-1,2,5-thiadiazolo-4-carboxylic acid derivatives by cleavage of the pyrimidine ring of [1,2,5]thiadiazolo-[3,4-*d*]pyrimidines (**13**) bearing amino and oxygen functions at position 7 or oxygen function at both positions 5 and 7 was reported in a series of papers by Shealy *et al.*<sup>17-21</sup> The reactions are analogous

<sup>17</sup> Y. F. Shealy, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.* **27**, 2154 (1962).

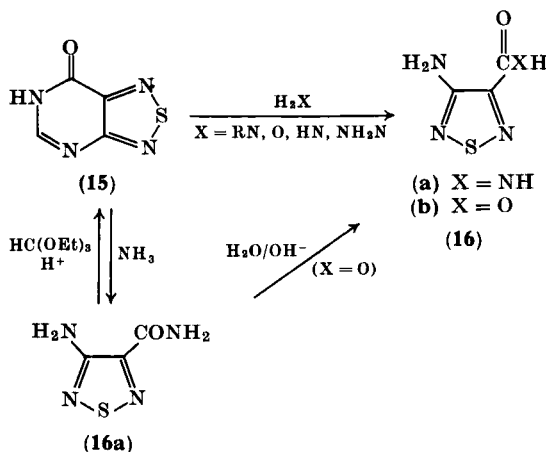
<sup>18</sup> Y. F. Shealy and J. D. Clayton, *J. Org. Chem.* **28**, 1491 (1963).

<sup>19</sup> Y. F. Shealy and C. A. O'Dell, *J. Org. Chem.* **29**, 2135 (1964).

<sup>20</sup> Y. F. Shealy and J. D. Clayton, *J. Org. Chem.* **29**, 2141 (1964).

<sup>21</sup> Y. F. Shealy and C. A. O'Dell, *J. Org. Chem.* **30**, 2488 (1965).

to the pyrimidine ring cleavage observed in the pteridine series (14) but generally occur under much milder conditions than those required for the pteridines. A variety of thiadiazole derivatives can be prepared by this method depending on the nature of the pyrimidine compound and the attacking base. The reaction of [1,2,5]thiadiazolo[3,4-*d*]-pyrimidin-7(6*H*)-one (15)<sup>18</sup> with ethanolic ammonia produced 3-amino-1,2,5-thiadiazole-4-carboxamide (16a) which reverted to 15

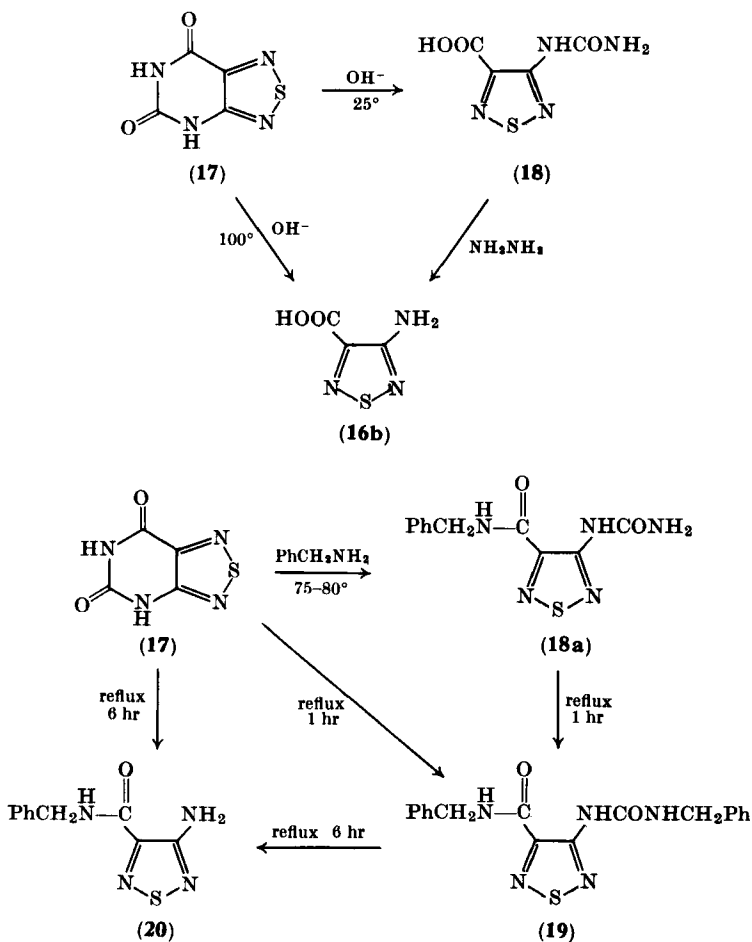


by reaction with ethyl orthoformate in presence of *p*-toluenesulfonic acid. Compound 16a was further characterized by conversion into the amino acid (16b) by aqueous base hydrolysis. Similar ring cleavage in 15 was achieved with aliphatic amines, hydrazine, aqueous potassium hydroxide, and aniline. The latter case required a trace of acid catalyst. In these reactions the site of base attack is position 7. However, analogous with the basic ring cleavage of 4-pteridones,<sup>22</sup> reaction was also observed at position 5. For example, the reaction of 15 with *n*-butylamine formed both the *N*-butylamide (16,  $X = nBuNH$ ) and the unsubstituted amide (16a). The latter product arises apparently by attack of 15 at position 5.

The 5,7-dione (17)<sup>20</sup> is cleaved by aqueous potassium hydroxide at room temperature to form the ureido derivative (18) in 87% yield. At 100° a mixture of 18 and the amino acid (16b) is obtained. The amino acid is the sole product when 18 is heated with base for extended

<sup>22</sup> E. C. Taylor, Jr., *Ciba Found. Symp., Chem. Biol. Pteridines*, 1954 pp. 2-34.

periods.<sup>23</sup> The ureido derivative is also smoothly converted to the amino acid by reaction with hydrazine.

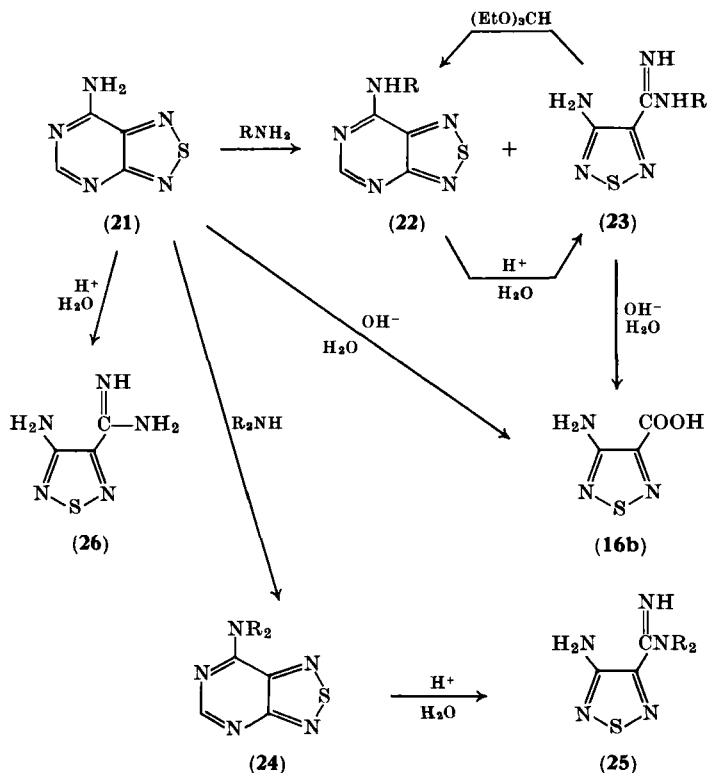


The reaction of the 5,7-dione (17) with primary amines led to the formation of three different thiadiazole derivatives depending on the reaction conditions.<sup>20</sup> The reaction with benzyl amine at  $75-80^\circ$  produced *N*-benzyl-4-ureido-1,2,5-thiadiazole-3-carboxamide (18a). Reaction of both 17 and 18a with benzylamine under reflux for 1 hour

<sup>23</sup> K. Menzl, Austrian Patent 230,885 (1963); *Chem. Abstr.*, **60**, 5513 (1964).



formed the dibenzyl compound (**19**). Finally under more drastic conditions (6.5-hour reflux) **17** as well as **19** yielded the amino-carboxamide derivative (**20**) and the by-product *N,N'*-dibenzylurea, both in high yield. Similar results were obtained by reaction of **17** with ethylamine, *n*-butylamine, and hydrazine.



In the course of an investigation of amino group exchange reactions of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidines (**21**) with primary amines, Shealy and O'Dell<sup>19</sup> isolated the ring-cleaved products **23** in addition to the amine exchange product **22**. Hydrolysis of the carbonyl compound **(23)** with aqueous alkali formed the amino acid (**16b**) which was also the product of direct basic hydrolysis of the amino pyrimidine (**21**). The reaction of **21** with secondary amines formed only the amine-exchanged product (**24**). Aqueous acid cleavage of the three aminopyrimidothiadiazole compounds represented in this system (**21**, **22**, **24**)

gave excellent yields of the corresponding unsubstituted, mono-, and disubstituted thiadiazole amidines (**26**, **23**, **25**).<sup>21</sup>

#### B. BY CYCLIZATION OF OPEN-CHAIN COMPOUNDS; GENERAL MODEL FOR THE CHOICE OF STARTING MATERIALS

The preparation of 1,2,5-thiadiazoles from bicyclic compounds discussed above is limited in that only the dicarboxylic acid and derivatives of the amino acid are accessible through these methods. A number of syntheses via cyclization of acyclic compounds have also been reported which lead to a variety of substituted derivatives such as alkyl, aryl, halo, hydroxy, alkoxy, and amino. A general model for the structure of starting materials useful in the synthesis of 1,2,5-thiadiazoles has been described in terms of an acyclic NCCN system in which the NC groups exist at several oxidation levels including amine, imine, cyanide, and oxime.<sup>24, 24a</sup> Aliphatic compounds containing these functionalities in any combination react with sulfur monochloride or sulfur dichloride to form an appropriately substituted thiadiazole. Aliphatic compounds that are based on this model include 1,2-diamines,  $\alpha$ -amino acid amides,  $\alpha$ -aminonitriles,  $\alpha$ -aminoamidines, alkylcyanoformimidates, dialkylloximidates,  $\alpha$ -dioximes, 2-isonitroso-oximes, 2-isonitroso amides, alkylloximidates, cyanogen, and 1-cyanoformamide, all of which are either readily prepared by published procedures or commercially available.

##### 1. From $\alpha$ -Diamines

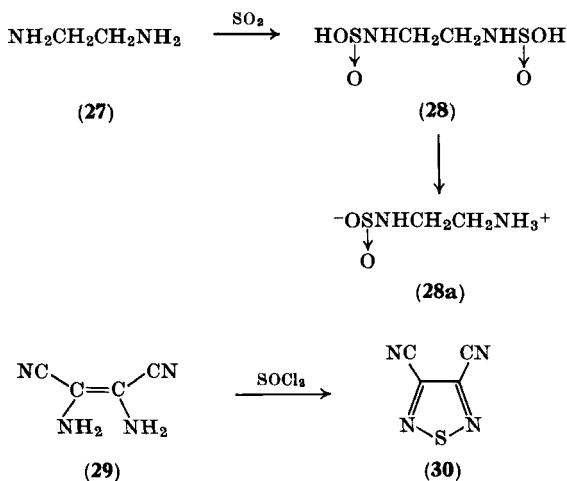
The synthesis of 1,2,5-thiadiazoles from  $\alpha$ -diamines was studied as early as 1897 when Michaelis<sup>25</sup> attempted the preparation of the parent compound by reaction of ethylenediamine with sulfur dioxide. The product, however, was bisulfimic acid (**28**) which readily lost sulfur dioxide to form the betaine (**28a**). Later Shew<sup>15</sup> reported that 3,4-dicyano-1,2,5-thiadiazole (**30**) results from the reaction of *cis*-diaminomaleonitrile (**29**, HCN tetramer) with thionyl chloride, a reaction which is analogous to 2,1,3-benzothiadiazole formation from *o*-phenylenediamines. The synthesis of the parent 1,2,5-thiadiazole and some alkyl analogs (**32**) was accomplished by reaction of salts of

<sup>24</sup> L. M. Weinstock, P. Davis, B. Handelsman, and R. Tull, *Tetrahedron Letters* p. 1263 (1966).

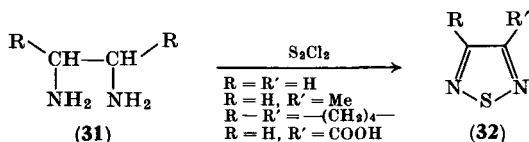
<sup>24a</sup> L. M. Weinstock, P. Davis, B. Handelsman, and R. Tull, *J. Org. Chem.* **32**, 2823 (1967).

<sup>25</sup> A. Michaelis and P. Graentz, *Chem. Ber.* **30**, 1009 (1897).

1,2-diamines (31) with sulfur monochloride in dimethylformamide.<sup>24, 24a</sup> Ethylenediamine dihydrochloride was converted into 1,2,5-thiadiazole in over 50 % yield by this method. 1,2,5-Selenadiazole can also be prepared by an analogous method using selenium monochloride.<sup>26</sup> It was subsequently reported that sulfur nitride ( $N_4S_4$ ) enters the same reaction with ethylenediamine but since this reagent



is prepared by the reaction of sulfur monochloride with ammonia there is no advantage over the direct sulfur monochloride procedure.



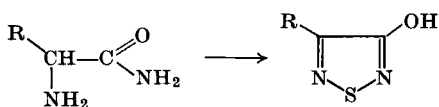
## 2. From $\alpha$ -Amino Acid Amides and Amidines

$\alpha$ -Amino acid amides, which fall into the amine-imine class according to the general model (beginning of Section II,B), are converted to 3-alkyl-4-hydroxy-1,2,5-thiadiazoles by reaction with sulfur monochloride,<sup>24, 24a</sup> thionyl chloride, or thionyl aniline. A large number of  $\alpha$ -amino acid amides were employed in the synthesis (see Table I)

<sup>26</sup> L. M. Weinstock, P. Davis, D. Mulvey, and J. Schaeffer, *Angew. Chem.* **79**, 315 (1967); *Angew. Chem. Intern. Ed. Engl.* **6**, 364 (1967).

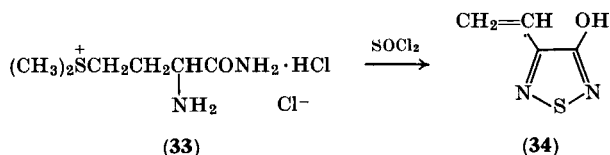
including glycine amide which forms 3-hydroxy-1,2,5-thiadiazole. In the reaction of methioninamide methylsulfonium chloride hydrochloride (33) with thionyl chloride, the resulting product was 3-hydroxy-4-vinyl-1,2,5-thiadiazole (34), dimethyl sulfide having been eliminated during the reaction.<sup>28</sup> Methioninamide hydrochloride reacted normally yielding the expected 3-hydroxy-4-methylmercaptoethyl-1,2,5-thiadiazole.

TABLE I  
3-ALKYL-4-HYDROXY-1,2,5-THIADIAZOLES FROM  
 $\alpha$ -AMINO ACID AMIDES



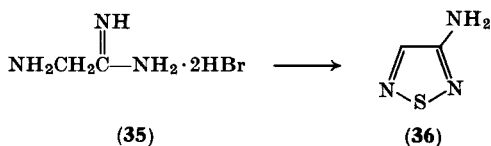
R	Amino acid amide used	Reference
H	Glycine amide	24, 27
Me	Alanine amide	24, 28
Et	$\alpha$ -Aminobutyramide	24
<i>n</i> -Pr	$\alpha$ -Aminovaleramide	24
iso-Pr	Valine amide	24, 28
<i>n</i> -Bu	$\alpha$ -Aminocaproamide	24
iso-Bu	Leucine amide	24
Ph	$\alpha$ -Aminophenylacetamide	24, 28
PhCH <sub>2</sub>	Phenylalanine amide	24, 28
CH <sub>3</sub> SCH <sub>2</sub> CH <sub>2</sub>	Methionine amide	28

In a related synthesis 3-amino-1,2,5-thiadiazole (36) was prepared from  $\alpha$ -aminoacetamidine dihydrobromide (35) and sulfur monochloride.<sup>24</sup> The relative inaccessibility of substituted  $\alpha$ -aminoamidines limits the usefulness of this method.



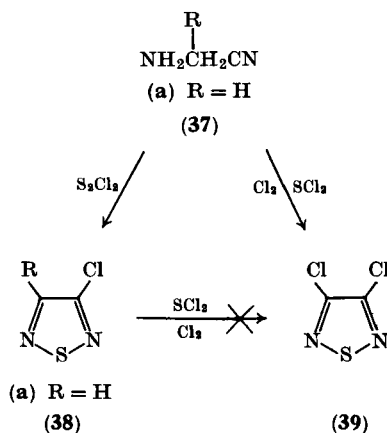
<sup>27</sup> G. R. Collins, Ph.D. Dissertation, Indiana University (1965); *Dissertation Abstr.* 27, 403-B (1966).

<sup>28</sup> S. A. Mizsak and M. Perelman, *J. Org. Chem.* 31, 1964 (1966).



### 3. From $\alpha$ -Aminonitriles

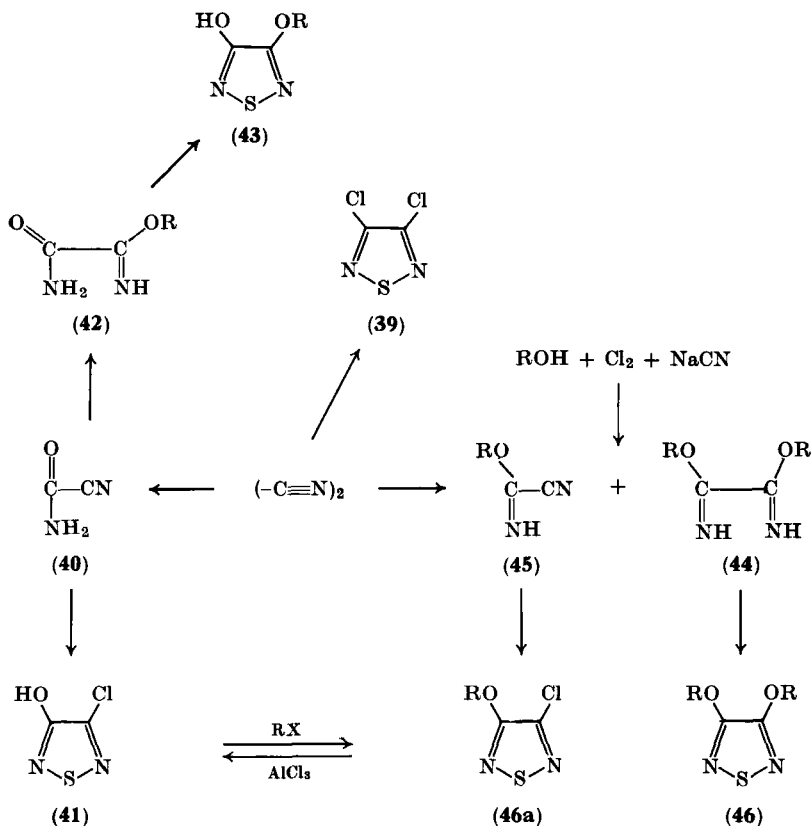
$\alpha$ -Aminonitriles (37) and their salts react with sulfur monochloride to form 3-chloro-4-alkylthiadiazoles (38). Best yields (75–80%) are obtained in reactions of 37 where R is hydrogen or phenyl; where R is alkyl the yields are poor.<sup>24, 24a</sup>



A modification of the reaction of  $\alpha$ -aminoacetonitrile (37a) has been developed which leads to 3,4-dichloro-1,2,5-thiadiazole (39) in over 80% yield.<sup>24a</sup> The action of commercial sulfur dichloride on 37a produces a 1-1 mixture of 3-chloro- and 3,4-dichloro-1,2,5-thiadiazole, (38 and 39). However, if excess chlorine is added to the reaction mixture the dichloro compound forms exclusively in 82% yield. It was shown that the dichloro compound does not form via chlorination of 3-chloro-1,2,5-thiadiazole. Therefore, either chlorination takes place on one of the intermediates prior to aromatization or the aminoacetonitrile is oxidized by the chlorine-sulfur dichloride mixture to cyanogen which is known to react with the sulfur chlorides to form 39 (see Section II, B, 4).

## 4. From Cyanogen and Cyanogen Derivatives

A number of useful syntheses of 1,2,5-thiadiazoles from cyanogen and its derivatives have been reported all of which proceed in high yield. 3,4-Dichloro-1,2,5-thiadiazole (39) was prepared by reaction of cyanogen with sulfur dichloride<sup>29</sup> or sulfur monochloride.<sup>24</sup> Unlike



sulfur dichloride, the reaction with sulfur monochloride is not exothermic and is readily carried out by simply passing cyanogen gas into a solution of the sulfur chloride in dimethylformamide at 80° and the product isolated in pure form in over 90% yield by steam distillation.

<sup>29</sup> R. D. Vest, U.S. Patent 3,115,497 (1963); *Chem. Abstr.* 60, 5512 (1964).

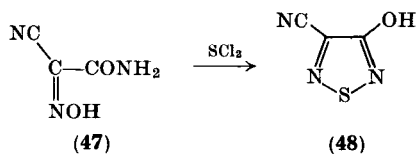
1-Cyanoformamide (**40**),<sup>30</sup> formed in quantitative yield by the acid-catalyzed reaction of cyanogen with water, is converted into 3-chloro-4-hydroxy-1,2,5-thiadiazole (**41**) by reaction with sulfur monochloride.<sup>24, 24a</sup> Prior conversion of **40** to the imino ether (**42**) leads to 3-ethoxy-4-hydroxy-1,2,5-thiadiazole (**43**).

The reaction products of cyanogen with alcohols, dialkyl oximides (**44**) and alkylcyanoformimidates (**45**), also available through the reaction of sodium cyanide with chlorine in aqueous alcohol,<sup>31</sup> both react with the sulfur chlorides forming the appropriately substituted thiadiazole. Wen<sup>16</sup> reported the synthesis of diethoxy-1,2,5-thiadiazole (**46**) from **44** and sulfur dichloride. Several analogs of **45** were converted to 3-chloro-4-alkoxy-1,2,5-thiadiazoles (**46a**) by treatment with sulfur monochloride.<sup>24, 24a</sup>

The interconversion of **41** and **46a** was effected by the alkylation of the hydroxy compound (**41**) and dealkylation of the chloro ethers (**46a**) with aluminum chloride.<sup>24a</sup>

### 5. From Oximes

Ross and Smith<sup>32</sup> prepared 3-cyano-4-hydroxy-1,2,5-thiadiazole (**48**) by the reaction of isonitrosocyanoacetamide (**47**) with sulfur dichloride.  $\alpha$ -Dioximes were also shown to enter the 1,2,5-thiadiazole



ring closure reaction<sup>24</sup> and by this method dimethylglyoxime (**49**) was converted into 3,4-dimethyl-1,2,5-thiadiazole (**50**) with sulfur monochloride. A trace by-product in this reaction was 3,4-dimethylfurazan which was shown by separate experiments not to be the intermediate in the thiadiazole formation.

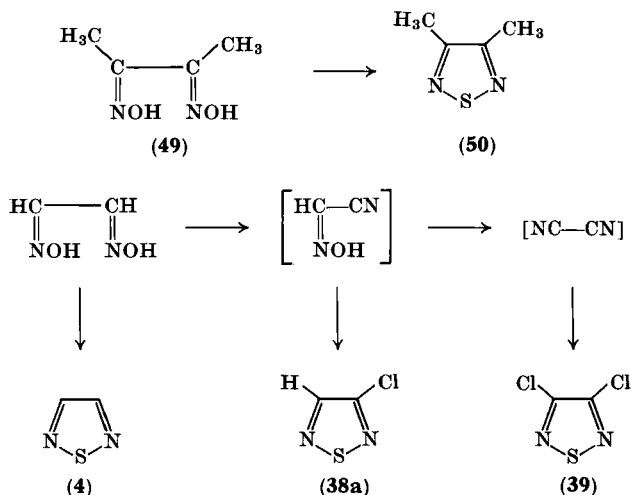
The reaction of aldoximes with sulfur monochloride is complicated by dehydration side reactions leading to nitrile intermediates and eventual chloro-containing thiadiazoles.<sup>24a</sup> Glyoxime and sulfur monochloride formed all three possible products, 1,2,5-thiadiazole

<sup>30</sup> R. D. Welcher, M. E. Castellion, and V. P. Wystrach, *J. Am. Chem. Soc.* **81**, 2541 (1959).

<sup>31</sup> J. U. Nef, *Ann. Chem.* **287**, 265 (1895).

<sup>32</sup> J. M. Ross and W. C. Smith, *J. Am. Chem. Soc.* **86**, 2861 (1964).

(4), 3-chloro-1,2,5-thiadiazole (38a, R = H), and 3,4-dichloro-1,2,5-thiadiazole (39), the latter two products resulting from the reaction of the dehydration intermediates cyanoformaldoxime and cyanogen.



#### 6. Mechanism of the Formation of 1,2,5-Thiadiazoles by Cyclization Methods

Based on previous work with sulfur monochloride, a reaction pathway leading to 1,2,5-thiadiazole from sulfur monochloride was postulated. Reactions of sulfur monochloride indicate that the molecule can be polarized as  $\text{ClSS}^{\delta+}-\text{Cl}^{\delta-}$  and in several instances compounds containing the chlorodithio group ( $\text{ClSS}-$ ) have been isolated.<sup>33</sup> Chlorodithio compounds have also been postulated as intermediates in the reaction of aliphatic amides with sulfur monochloride leading to bisamidodisulfides<sup>34</sup> and in the Herz reaction.<sup>35</sup> It has also been reported that under the conditions of the Herz reaction *o*-phenylenediamine is converted to 2,1,3-benzothiadiazole<sup>36</sup> and in this case it appears that the intermediate *N*-chlorodithio compound is cleaved at the S—S bond by nucleophilic attack by the ortho amino group, Eq. (1). A similar process was proposed for the formation of

<sup>33</sup> Z. S. Ariyan and L. A. Wiles, *J. Chem. Soc.*, 4510 (1961); 1725 (1962); 755 (1963).

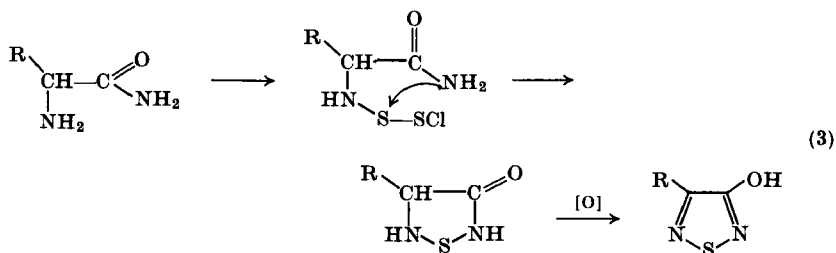
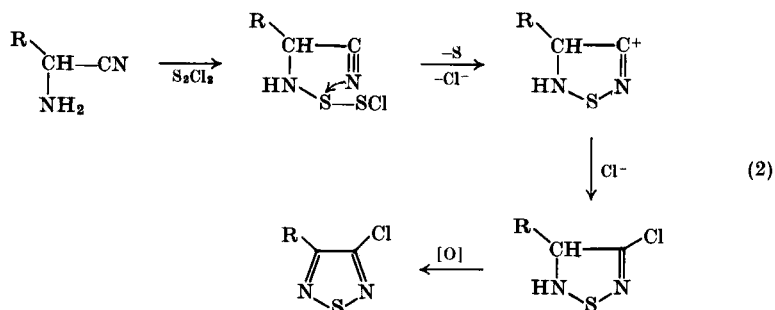
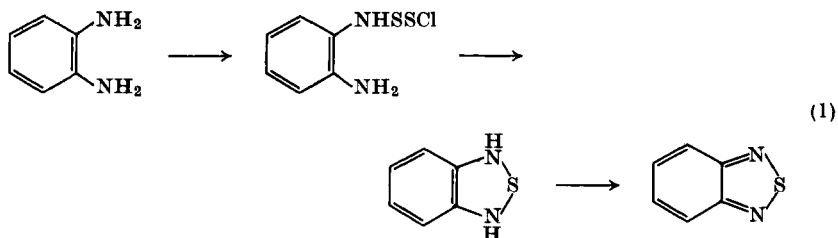
<sup>34</sup> P. Hope and L. A. Wiles, *J. Chem. Soc.*, 5679 (1964).

<sup>35</sup> P. Hope and L. A. Wiles, *Chem & Ind. (London)*, 32 (1966).

<sup>36</sup> P. Hope and L. A. Wiles, *J. Chem. Soc., C. Org.*, 1283 (1966).



monocyclic 1,2,5-thiadiazoles from aliphatic compounds and sulfur monochloride. The reactions of  $\alpha$ -aminonitriles, Eq. (2), and  $\alpha$ -amino acid amides, Eq. (3), serve to illustrate the role of the amine, amide, and cyanide functions in these cyclizations. The formation of thiadiazoles from oximes is less easily rationalized.



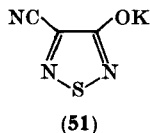
From Eq. (3) it is clear that amine functions applicable in these syntheses must be primary and bear at least one  $\alpha$ -hydrogen atom. This allows oxidation to the aromatic form of the thiadiazole, presumably via *N*-chloro or *N*-chlorodithio intermediates. Sulfur monochloride or adjacent *N*-chlorodithio groups, shown in Eq. (2), react with nitrile groups by addition leading to chloro substituted 1,2,5-thiadiazoles.

Since sulfur dichloride is in equilibrium with sulfur monochloride and chlorine, the reagents behave in the same manner except that the presence of chlorine leads to the introduction of an additional chlorine atom in the thiadiazole in certain cases where the dichloride is employed. The mechanism of formation of bicyclic 1,2,5-thiadiazoles from ortho-aromatic diamines and thionyl chloride or thionyl aniline was discussed by Shealy *et al.*<sup>17</sup>

### C. MISCELLANEOUS SYNTHESSES

#### 1. *By Reaction of Sulfur Dioxide with Potassium Cyanide*

A unique thiadiazole synthesis from the industrial raw materials sulfur dioxide and potassium cyanide has been reported by Ross and



Smith.<sup>32, 37, 38</sup> These reagents react under anhydrous conditions, either in acetonitrile at atmospheric pressure or in absence of an organic solvent under autogenous pressure, to form 40–50 % of the potassium salt of 3-hydroxy-4-cyano-1,2,5-thiadiazole (51). Potassium pyrosulfite is formed as one of the by-products. It is interesting to note that the reaction of sulfur dioxide and potassium cyanide in aqueous media was studied as early as 1879<sup>39</sup> and reinvestigated under anhydrous conditions by a number of workers since that time. Except for the work of Ross and Smith the products isolated were largely inorganic.

#### 2. *From Ethylaromatic Hydrocarbons*

Sulfur nitride ( $N_4S_4$ ) reacts with ethyl-substituted aromatic hydrocarbons forming aryl thiadiazoles.<sup>40</sup> While the yields are low (6–12 %) the method is of value because of the simplicity of the organic starting

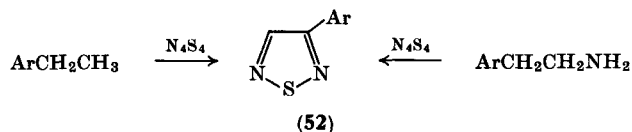
<sup>37</sup> J. M. Ross and W. C. Smith, U.S. Patent 3,068,238 (1962); *Chem. Abstr.* **58**, 10207 (1963).

<sup>38</sup> J. M. Ross and W. C. Smith, U.S. Patent 3,117,972 (1964); *Chem. Abstr.* **60**, 6851 (1964).

<sup>39</sup> A. Étard, *Compt. Rend.* **88**, 649 (1879).

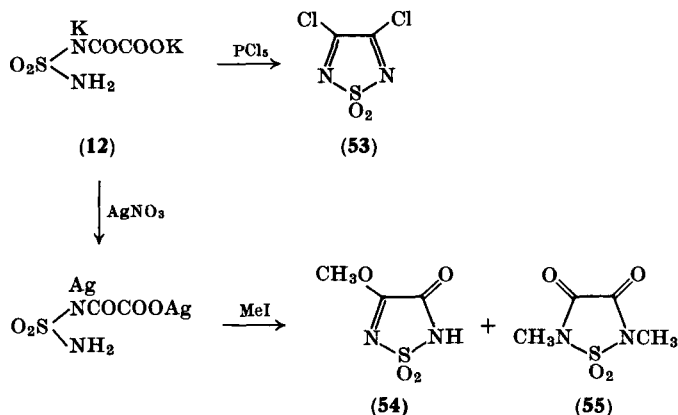
<sup>40</sup> V. Bertini and P. Pino, *Angew. Chem.* **77**, 262 (1965); *Angew. Chem. Intern. Ed. Engl.* **4**, 239 (1965).

materials. Ethylbenzene, 1,2-diphenylethane, and  $\beta$ -ethylnaphthalene were employed in the reaction, forming 3-phenyl- (52), 3,4-diphenyl-, and 3- $\beta$ -naphthyl-1,2,5-thiadiazole, respectively. Amine-substituted ethylaromatic hydrocarbons such as  $\beta$ -phenethylamine also enter the reaction and in these cases the yields are higher.<sup>41</sup>



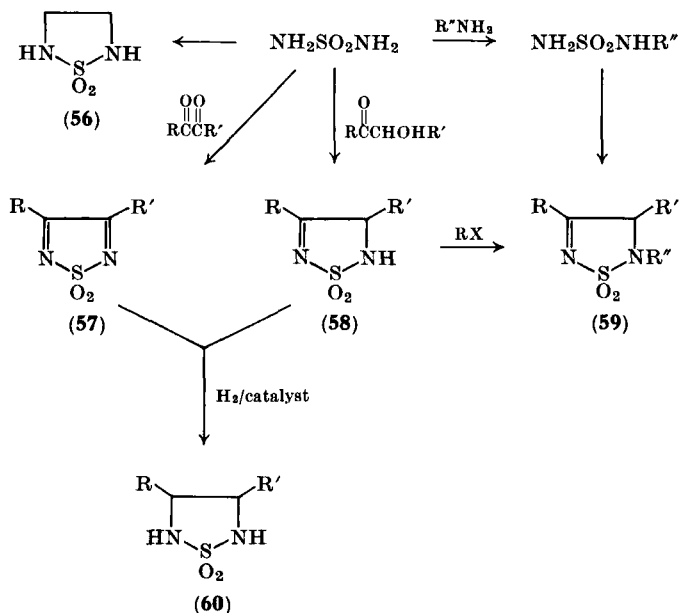
#### D. SYNTHESIS OF 1,2,5-THIADIAZOLE-1,1-DIOXIDES AND REDUCED FORMS OF 1,2,5-THIADIAZOLE

Wen<sup>16</sup> found that *N*-sulfamoyloxamic acid (12), a by-product formed during the permanganate oxidation of 2,1,3-benzothiadiazole (Section II, A, 1), can be converted into 3,4-dichloro-1,2,5-thiadiazole-1,1-dioxide (53) by reaction with phosphorus pentachloride. Other thiadiazole-1,1-dioxides that were derived from 12 by methylation of its disilver salt include 2-methyl-3-oxo-4-methoxy-1,2,5-thiadiazoline-1,1-dioxide (54) and 2,5-dimethyl-3,4-dioxo-1,2,5-thiadiazolidine-1,1-dioxide (55).



<sup>41</sup> V. Bertini and P. Pino, *Angew. Chem.* **78**, 493 (1966); *Angew. Chem. Intern. Ed. Engl.* **5**, 514 (1966).

The direct formation of disubstituted 1,2,5-thiadiazole-1,1-dioxides (**57**) by condensation of  $\alpha$ -diketones with sulfamide was reported by Wright<sup>42-45</sup> and by Vorreither and Ziegler.<sup>46</sup> The 1,2,5-thiadiazoline-1,1-dioxides (**58**) were prepared by a similar method employing  $\alpha$ -hydroxy ketones. Hydrogenation of both **57** and **58** over Adams catalyst provided the corresponding disubstituted 1,2,5-thiadiazolidine-1,1-dioxides (**60**).<sup>42</sup> 2-Alkyl-1,2,5-thiadiazoline-1,1-dioxides (**59**) were obtained either by alkylation of **58** or by direct



condensation of an  $\alpha$ -hydroxy ketone with an *N*-alkylated sulfamide derivative. The parent 1,2,5-thiadiazolidine-1,1-dioxide (**56**) was synthesized from ethylenediamine and sulfamide<sup>47</sup> but neither the parent thiadiazole-1,1-dioxide nor any of its monosubstituted derivatives has been reported.

<sup>42</sup> J. B. Wright, *J. Org. Chem.* **29**, 1905 (1964).

<sup>43</sup> J. B. Wright, U.S. Patent 3,115,495 (1963); *Chem. Abstr.*, **60**, 5513 (1964).

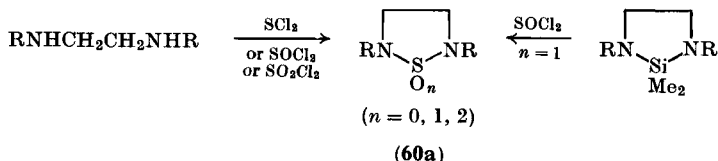
<sup>44</sup> J. B. Wright, U.S. Patent 3,115,496 (1963); *Chem. Abstr.* **60**, 5512 (1964).

<sup>45</sup> J. B. Wright, U.S. Patent 3,186,998 (1965); *Chem. Abstr.* **63**, 13275 (1965).

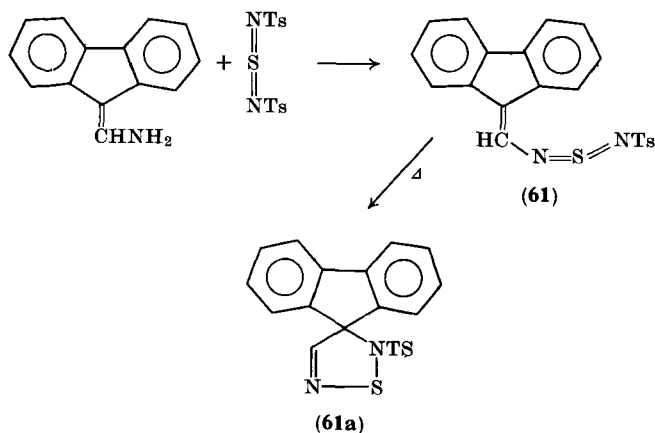
<sup>46</sup> H. K. Vorreither and E. Ziegler, *Monatsh. Chem.* **96**, 216 (1965).

<sup>47</sup> A. Ciaperoni, A. Vandi, G. Stea, G. B. Gechele, and B. Minasso, *Chim. Ind. (Milan)* **47**, 1200 (1965); *Chem. Abstr.* **64**, 6645 (1966).

Several related 1,2,5-thiadiazolidines have been synthesized from *N,N'*-dialkylethylenediamines by condensation with sulfur dichloride, thionyl chloride, and sulfuryl chloride.<sup>48</sup> These reagents produced the thiadiazolidines **60a**,  $n = 0, 1$ , and  $2$ , respectively. A siladiazolidine was converted into **60a** ( $n = 1$ ) by treatment with thionyl chloride.<sup>49</sup>



1,2,5-Thiadiazolines were prepared by 1,5-cyclization of vinyl-substituted sulfur diimides.<sup>50</sup> Thus, condensation of 9-(aminomethylene)fluorene with bis(*p*-toluenesulfonyl)sulfur diimide produced the intermediate **61** which was converted to the thiadiazoline (**61a**) on heating. The 3,3-diphenyl analog of **61a** was similarly prepared.



### III. Chemical Properties of 1,2,5-Thiadiazoles

#### A. STABILITY OF THE 1,2,5-THIADIAZOLE NUCLEUS

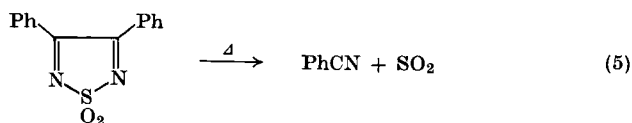
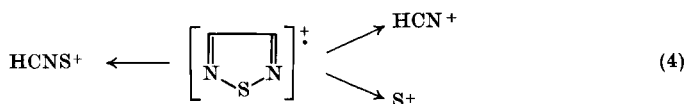
The 1,2,5-thiadiazoles are very stable thermally. The unsubstituted ring is unchanged on heating at  $220^\circ$  and it has been reported that the

<sup>48</sup> S. Melamed and W. L. Croxall, U.S. Patent 2,624,729; *Chem. Abstr.* **47**, 11256 (1953).

<sup>49</sup> E. W. Abel and R. P. Bush, *J. Organometal. Chem. (Amsterdam)* **3**, 245 (1965).

<sup>50</sup> G. Kresze and C. Seyfried, *Angew. Chem.* **78**, 1061 (1966).

potassium salt of 3-cyano-4-hydroxy-1,2,5-thiadiazole is stable up to  $360^{\circ}$ .<sup>36</sup> At  $400^{\circ}$  the potassium salt fragments and sulfur, cyanogen, potassium cyanide, potassium thiocyanate, and traces of oxygen were found among the principal decomposition products. The stability of the 1,2,5-thiadiazole nucleus is also indicated in its 70-ev mass spectrum which displays the molecular ion ( $m/e$  86) as the major peak in addition to several fragmentation ions.<sup>51</sup> The fragmentation of 1,2,5-thiadiazole under electron impact, Eq. (4), is analogous to that observed for 1,2,5-oxadiazole (furazan)<sup>52</sup> and 1,2,5-selendiazole.<sup>26</sup>



The 1,2,5-thiadiazole-1,1-dioxides are less stable toward heat. At its melting point ( $250^{\circ}$ ) 3,4-diphenyl-1,2,5-thiadiazole-1,1-dioxide is decomposed to benzonitrile and sulfur dioxide, among other unidentified products, Eq. (5).<sup>53</sup>

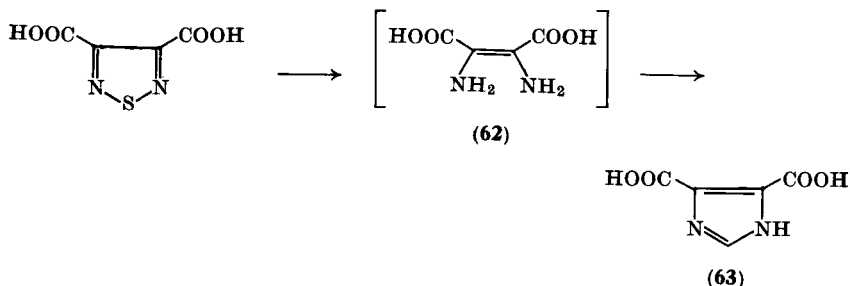
Some sensitivity of the 1,2,5-thiadiazole nucleus toward oxidizing agents has been noted. Oxidation of 2,1,3-benzothiadiazoles with potassium permanganate, while producing good yields of 1,2,5-thiadiazole-3,4-dicarboxylic acid, leads to low yields of side products which indicate reaction at the sulfur atom (Section II,A,1). Permanganate oxidation of 3-phenylthiadiazole, on the other hand, results in total degradation of the thiadiazole ring with formation of benzoic acid in 80% yield.<sup>41</sup> Oxidation of both bicyclic and monocyclic thiadiazoles with peracids is usually accompanied with ring destruction and formation of sulfate ion.<sup>11</sup> Attempts to prepare 1,2,5-thiadiazole-1,1-dioxide by peracetic acid oxidation of the parent ring resulted in ring cleavage analogous to the results obtained with 1,2,4- and 1,3,4-thiadiazole.<sup>8</sup>

<sup>51</sup> F.-H. Marquardt, Ph.D. Dissertation, Indiana University (1960); *Dissertation Abstr.* **21**, 3272 (1961).

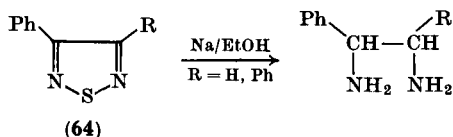
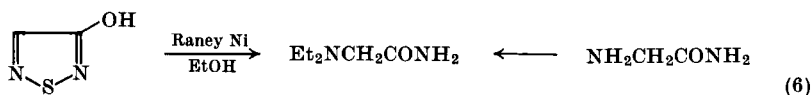
<sup>52</sup> R. A. Olofson and J. S. Michelman, *J. Org. Chem.* **30**, 1854 (1965).

<sup>53</sup> J. Schaeffer, unpublished results (1966).

The 1,2,5-thiadiazole ring is susceptible to reductive cleavage by a number of reagents including zinc and mineral acids,<sup>15</sup> sodium and alcohol,<sup>41</sup> and Raney nickel.<sup>32</sup> Reduction occurs at the N—S bond (also the site of cleavage of 1,2,3- and 1,2,4-thiadiazoles) with formation of hydrogen sulfide and regeneration of the NCCN portion of the molecule in a reduced form. This property has been employed as a method of structure proof of 1,2,5-thiadiazoles in a number of cases.



1,2,5-Thiadiazole-3,4-dicarboxylic acid was reduced with tin and hydrochloric acid to diaminomaleic acid (62), which, without isolation, was converted into the known imidazoledicarboxylic acid (63) by reaction with formic acid.<sup>11</sup>

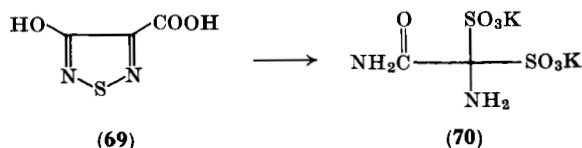
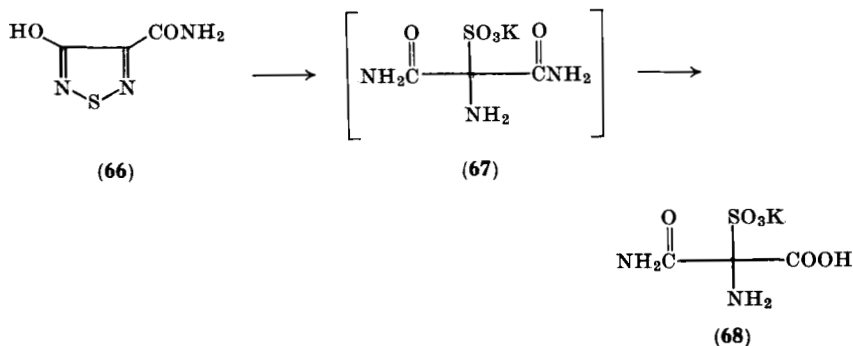
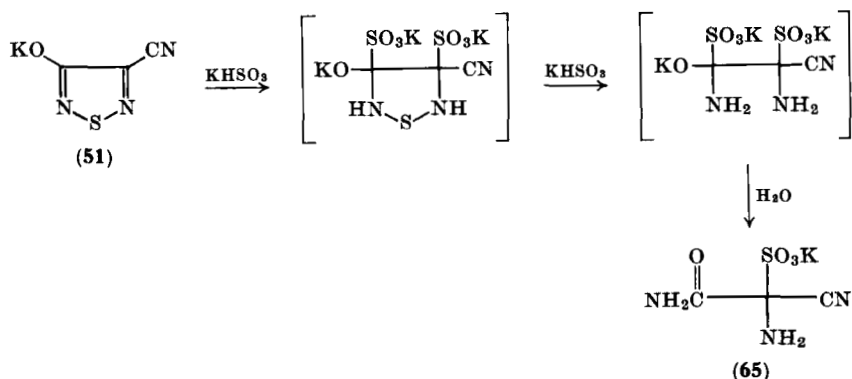


The skeletal structure of 3-hydroxy-1,2,5-thiadiazole was determined through reductive desulfurization with Raney nickel in ethanol which formed *N,N*-diethylaminoacetamide, Eq. (6). The same product was obtained by subjecting the proposed intermediate, glycynamide, to the same reaction conditions.<sup>32</sup> The aryl-substituted thiadiazoles (64) were reduced to  $\alpha$ -diamines with sodium and alcohol.<sup>41</sup>

Ross<sup>54</sup> reported that hydroxythiadiazole derivatives rapidly

<sup>54</sup> J. M. Ross, *J. Am. Chem. Soc.* **86**, 2869 (1964).

undergo reductive cleavage in warm aqueous potassium bisulfite solution. The product of the reaction of the potassium salt of 3-hydroxy-4-cyano-1,2,5-thiadiazole (**51**) was potassium aminocarbamoyl-cyanomethylsulfonate (**65**) which formed via addition of two mole-



cules of bisulfite to the C=N linkages of **51** followed by reduction of the N—S bonds with additional bisulfite. The hydroxyamide (**66**) reacted similarly but the product in this case was the potassium salt of aminocarbamoylcarboxymethanesulfonate (**68**), resulting from partial hydrolysis of the expected diamide (**67**). The hydroxyacid (**69**)



took another course and decarboxylation with concurrent sulfo group migration in the bisulfite addition intermediate led to the formation of the dipotassium salt of aminocarbamoylmethionate (70). Analogous bisulfite addition reactions have been observed in a number of other  $\pi$ -electron-deficient *N*-heterocyclic systems, e.g., quinoxalines, acridines, pyrimidines, and pteridines.<sup>55</sup> In these cases the addition products do not undergo cleavage but revert to the aromatic form of the heterocycle by treatment with acid or base.

The polarographic reductive behavior of 1,2,5-thiadiazoles is discussed in Section V,C.

The 1,2,5-thiadiazole nucleus is stable to both dilute and concentrated mineral acids and to Lewis acids. Certain derivatives, however, are decomposed slowly by base. No decomposition of the parent 1,2,5-thiadiazole was detected after 16 hours at 25° in 1 *N* sodium hydroxide while at 80° approximately 30% of the material decomposed in 1 hour. This contrasts with the oxygen analog, furazan, and the monosubstituted furazans which are rapidly decomposed by cold aqueous base to  $\alpha$ -cyanooximes. Mono- and dimethyl thiadiazole are both stable in 1 *N* sodium hydroxide up to 80° but the monochloro and dichloro derivatives are both degraded more rapidly than the unsubstituted compound. Thiadiazoles bearing acidic functions (the hydroxy, carboxy, and sulfonamide derivatives) exhibit complete base stability. In general, 1,2,5-thiadiazoles can be employed in reactions carried out in basic media provided drastic conditions are not required.

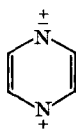
## B. BASICITY OF THE 1,2,5-THIA DIAZOLE NUCLEUS

The 1,2,5-thiadiazole nucleus is extremely weakly basic and exhibits an ultraviolet spectrum in concentrated hydrochloric acid identical to that in water. A bathochromic shift of 9  $m\mu$  in the spectrum taken in 96% sulfuric acid indicates some protonation of the ring in that solvent.<sup>51</sup> 1,2,5-Thiadiazole is a much weaker base than pyrazine ( $pK_a$  0.6) and probably has a  $pK_a$  well below zero. The very low basicity of pyrazine was explained by Albert *et al.*<sup>56</sup> as being related to the

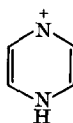
<sup>55</sup> A. Albert, *Current Trends Heterocyclic Chem., Proc. Symp., Canberra, 1957* Chapter 4, p. 20. Academic Press, New York, 1958.

<sup>56</sup> A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

contribution of exactly equivalent dipolar structures in the non-ionized molecule (71) which strengthens the resonance of this species at the expense of the ion whose structure (72) is of little importance. A similar explanation can be applied to the thiadiazole case. Two salts of 1,2,5-thiadiazole, the sulfate and perchlorate, and two metal complexes, the mercury(II) chloride and silver(I) nitrate, have been reported. The products are unstable and undergo extensive dissociation even in the absence of moisture.<sup>51</sup> Except for the 3,4-dimethyl derivative, 1,2,5-thiadiazoles are readily extracted from strongly acidic aqueous media with organic solvents.



(71)



(72)

### C. ELECTROPHILIC AND NUCLEOPHILIC SUBSTITUTION

1,2,5-Thiadiazole generally resists electrophilic substitution. The compound is inert under various conditions of halogenation and nitration, and fails to enter the Friedel-Crafts reactions with benzoyl chloride and aluminum chloride.<sup>8, 51</sup> An electrophilic deuteration of 1,2,5-thiadiazole was accomplished in low yield by heating with phosphoric acid-*d*<sub>3</sub> at 250°. <sup>51</sup> Some examples of electrophilic substitution of monosubstituted 1,2,5-thiadiazoles containing activating groups are known. The halogenation of 3-amino-1,2,5-thiadiazole takes place readily in acetic acid at room temperature and both the nuclear substituted bromo- and chloroamine were prepared in this manner.<sup>57</sup> Also, 3-methyl-1,2,5-thiadiazole is slowly chlorinated at 25° to 3-chloro-4-methyl-1,2,5-thiadiazole in acetonitrile solution.<sup>58</sup>

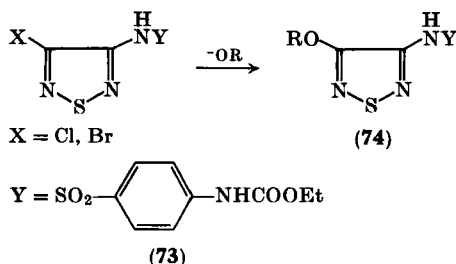
Nucleophilic substitution of halogen substituents occurs readily in the 1,2,5-thiadiazole series. The chloro- and bromosulfanilamide derivatives (73) were converted into ethers (74) in high yield by simply refluxing with alkoxides dissolved in the corresponding alcohol.<sup>57</sup> The reaction of chlorothiadiazole with ammonia at 100° and with

<sup>57</sup> K. Menzl, German Patent 1,175,683 (1964); *Chem. Abstr.* **61**, 12009 (1964); see also U.S. Patent 3,247,193 (1966).

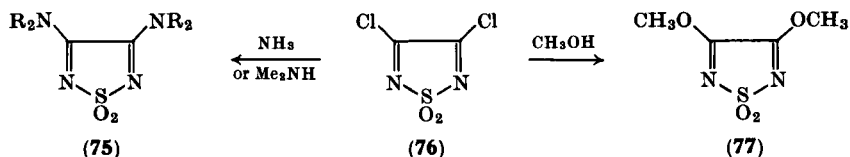
<sup>58</sup> P. Davis, unpublished results (1965).

sulfanilamide and base at 140° formed aminothiadiazoole and sulfathiadiazoole, respectively. The yields in these reactions were low (20–30%) due to the sensitivity of chlorothiadiazoole to base.<sup>24a</sup>

The observation has been made that the 1,2,5-thiadiazoole-1,1-dioxide nucleus behaves like a strong acyl function and that the dichloro (76), dimethoxy (77), and diamino (75) derivatives are in fact an acid chloride, ester, and amide of a strong acid.<sup>16</sup> The dichloro (76) compound is highly reactive toward nucleophiles and must be



protected from atmospheric moisture to avoid hydrolysis of the chloro groups. The reaction of 76 with methanol does not require base catalysis and is complete after 15 minutes at reflux; with ammonia and dimethylamine the reaction is instantaneous. Even the dimethoxy compound (77) exhibits a high degree of reactivity with bases and enters a reaction with ammonia in methanol which is complete after 1 hour at room temperature.



Although 3,4-dichloro-1,2,5-thiadiazoole-1,1-dioxide (76) is related structurally to 3,4-dichlorothiophene-1,1-dioxide their chemical properties are quite different. The thiophene compound is a reactive diene and readily dimerizes via an auto Diels–Alder reaction.<sup>59</sup> Furthermore, its chlorine atoms are unreactive toward weak nucleophilic reagents like water and alcohol. The thiadiazoole compound, on the other hand, shows no tendency to dimerize and is highly reactive toward water and alcohol.

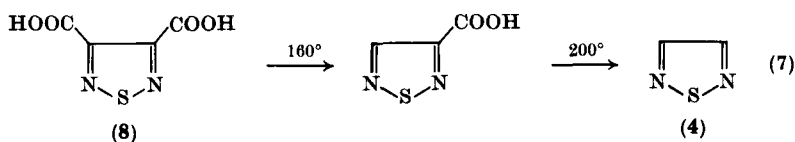
<sup>59</sup> H. Bluestone, R. Bimber, R. Berkey, and Z. Mandel, *J. Org. Chem.* **26**, 346 (1961).

## D. 1,2,5-THIA DIAZOLE CARBONYL DERIVATIVES

1. *Carboxylic Acids*

The mono- and dicarboxylic acids and their derivatives were among the earliest available thiadiazoles and have been the subject of a considerable amount of investigation. The acids are readily converted to reactive esters, acid chlorides, amides, hydrazides, and nitriles<sup>3, 14, 15, 60, 61</sup> which are useful starting materials in many reactions leading to key thiadiazoles including the methyl and substituted methyl, aldehyde and ketone, olefinic, and amine derivatives. Thiadiazole dicarboxylic acid forms a very unstable bicyclic anhydride which is not readily isolated.<sup>51</sup>

The pronounced electron-withdrawing nature of the 1,2,5-thiadiazole ring is evidenced by the fact that its carboxylic acid derivatives are highly acidic.<sup>8, 14</sup> The titration curve of the dicarboxylic acid exhibits two breaks with  $pK_{a1}$  and  $pK_{a2}$  equal to 1.59 and 4.14, respectively. The monocarboxylic acid is also strongly acidic and has a  $pK_a$  of 2.47, comparable to that of *ortho*-nitrobenzoic acid ( $pK_a$  2.18) and pyrazine-2-carboxylic acid ( $pK_a$  2.80). In general the  $pK_a$  values for the thiadiazole carboxylic acids are in fair agreement with the  $pK_a$ 's of the corresponding pyrazine acids (see Table II).



The thiadiazolecarboxylic acids are readily decarboxylated in the temperature range of 160–200° in the absence of catalysts. The stepwise decarboxylation of the dicarboxylic acid provided the monocarboxylic acid and the parent compound, 1,2,5-thiadiazole, both in good yield, Eq. (7).<sup>8, 9</sup> Decarboxylation has proved a valuable method for the syntheses of simple monosubstituted derivatives and both 3-amino<sup>57</sup> and 3-hydroxy-1,2,5-thiadiazole<sup>32</sup> were obtained from the corresponding acids. A convenient method for the preparation of

<sup>60</sup> M. Carmack, D. Shew, and L. M. Weinstock, U.S. Patent 2,990,409 (1961); *Chem. Abstr.* **56**, 4775 (1962).

<sup>61</sup> M. Carmack, D. Shew, and L. M. Weinstock, U.S. Patents 3,014,914 and 3,014,915 (1961).

TABLE II  
DISSOCIATION CONSTANTS OF THE 1,2,5-THIADIAZOLE CARBOXYLIC  
ACIDS AND RELATED COMPOUNDS IN WATER

Compound	pK <sub>a1</sub>	pK <sub>a2</sub>	Reference
1,2,5-Thiadiazole-3,4-dicarboxylic acid	1.59	4.14	8
1,2,5-Thiadiazole-3-carboxylic acid	2.47	—	8, 14
3-Amino-1,2,5-thiadiazole-4-carboxylic acid	3.22	—	51
3-Hydroxy-1,2,5-thiadiazole-4-carboxylic acid	2.57	6.73	32
Pyrazine-2,3-dicarboxylic acid	1.83	3.45	8
Pyrazine-2-carboxylic acid	2.80	—	8
2-Aminopyrazine-3-carboxylic acid	3.40	—	62
2-Hydroxypyrazine-3-carboxylic acid	3.10	8.57	62
Pyridine-2-carboxylic acid	5.30	—	63
<i>o</i> -Nitrobenzoic acid	2.16	—	63

deuterated thiadiazole was developed which involves decarboxylation of the deuterated acid. 1,2,5-Thiadiazole-*d*<sub>2</sub> of very high isotopic purity was obtained by this method.<sup>51</sup>

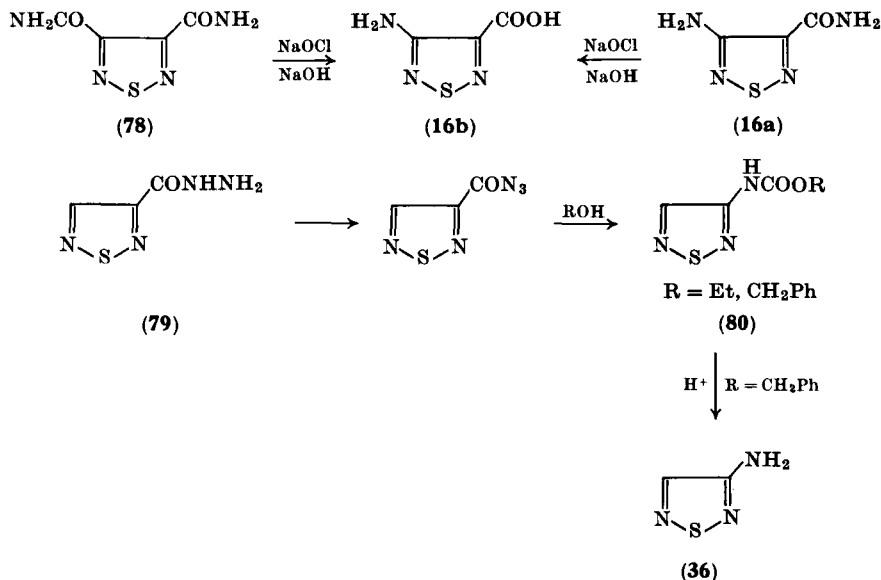
## 2. Acid Chlorides, Amides, and Hydrazides

The Hofmann and Curtius reactions as applied to both the mono- and diamides and hydrazides have been reported. Marquardt<sup>51</sup> found that a low yield of the amine can be obtained in the Hofmann reaction of 1,2,5-thiadiazole-3-carboxamide. The main side reaction was hydrolysis of the electron-deficient amide to the carboxylic acid. Under the same conditions the dicarboxamide (**78**) formed the amino acid (**16b**).<sup>16</sup> Attempts to prepare diaminothiadiazole via the Hofmann reaction of the amino amide (**16a**) resulted only in amide hydrolysis and the formation of the same amino acid.

<sup>62</sup> L. M. Weinstock, unpublished results (1966).

<sup>63</sup> R. W. Weast, ed., "Handbook of Chemistry and Physics," 45th ed., p. D-77. Chem. Rubber Publ. Co., Cleveland, Ohio, 1964.

The Curtius reaction of 1,2,5-thiadiazole-3-carbohydrazide (**79**) proceeded normally and in high yield to the ethyl urethane (**80**, R = Et). The ethyl urethane, however, resisted acid hydrolysis and was extensively decomposed by base.<sup>64</sup> The benzyl urethane (**80**, R = CH<sub>2</sub>Ph), on the other hand, was smoothly hydrolyzed to the amine with aqueous acid.<sup>27</sup> Attempts to prepare 1,2,5-thiadiazole-3,4-dicarboxazide from the dihydrazide resulted in an unstable product which exploded violently.<sup>16</sup>



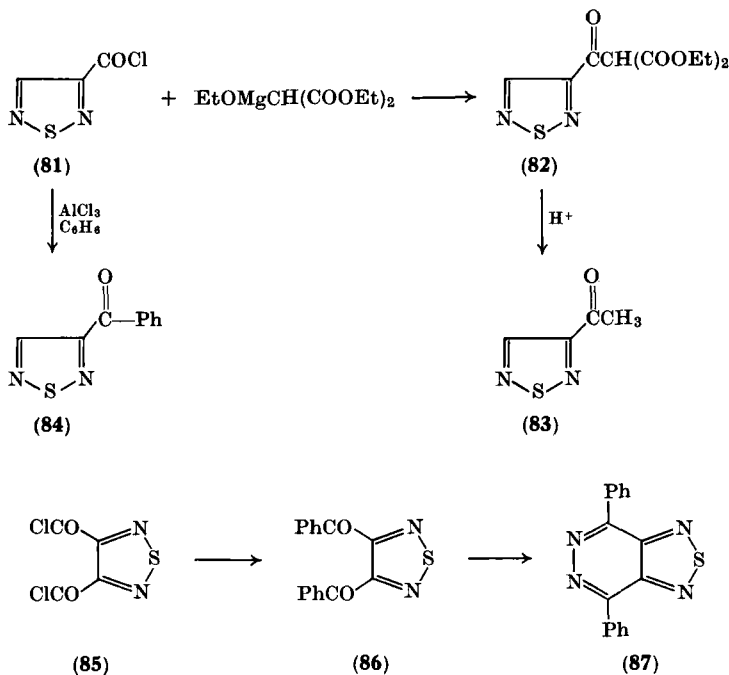
Three methods for the conversion of 3-chlorocarbonyl-1,2,5-thiadiazole (**81**) to ketones were investigated by Gill.<sup>65</sup> The Lund procedure<sup>66</sup> for the malonic ester synthesis of ketones proved quite successful for the preparation of 3-acetyl-1,2,5-thiadiazole (**83**). Condensation of **81** with diethyl ethoxymagnesiummalonate provides the ketodiester (**82**) which undergoes acid hydrolysis and decarboxylation to **83** in 90% yield. The same reaction sequence employing the sodio derivative of malonic ester was much less efficient.

<sup>64</sup> M. Carmack and L. M. Weinstock, U.S. Patent 3,060,187 (1962); *Chem. Abstr.* **58**, 9089 (1963).

<sup>65</sup> J. M. Gill, Ph.D. Dissertation, Indiana University (1963); *Dissertation Abstr.* **24**, 2690 (1964).

<sup>66</sup> H. Lund, *Chem. Ber.* **67**, 935 (1934).

The aluminum chloride-catalyzed Friedel-Crafts reaction of **81** and benzene produced benzoylthiadiazole (**84**) in almost quantitative yield.<sup>25, 65</sup> The product of the Friedel-Crafts reaction of benzene and 3,4-bis(chlorocarbonyl)-1,2,5-thiadiazole (**85**) is the nonrearranged dibenzoylthiadiazole (**86**).<sup>25</sup> The material, therefore, does not behave



like phthaloyl chloride which rearranges with aluminum chloride to dichlorophthalide and yields diphenylphthalide as the Friedel-Crafts product. The structure of dibenzoylthiadiazole was indicated in its conversion to the pyridazothiadiazole (**87**) on treatment with hydrazine.

A detailed study of the synthesis of thiadiazole ketones via the reaction of 3-chlorocarbonyl-1,2,5-thiadiazoles with dialkylcadmium reagents was reported.<sup>65</sup> In each case the ketone was obtained in only low yield, the major product being a tertiary carbinol or a tertiary carbinol dehydration product. These products stemmed from the reaction of the desired ketone with a second equivalent of the cadmium reagent. Thus, the 1,2,5-thiadiazole ketones are among the very few

ketones known which are not readily prepared by the dialkylcadmium method by virtue of their high reactivity toward the reagent. It has been shown that the reactivity of dialkylcadmium reagents is related to a large degree to the presence of magnesium salts formed during their usual preparation by the metathetical reaction of Grignard reagents with cadmium halides.<sup>67</sup> It was further demonstrated that replacement of these magnesium salts with weaker activating lithium bromide results in a reagent which is more selective toward reaction with acid chlorides<sup>68</sup> in presence of activated ketones. Use of this regulated reagent in the thiadiazole case could result in higher yields of the desired ketones.

Reduction of 3-chlorocarbonyl-1,2,5-thiadiazole (**81**) with sodium or lithium borohydride yielded 80% of 3-hydroxymethyl-1,2,5-thiadiazole with no ring desulfurization noted. Approximately the same results were obtained in the lithium aluminum hydride reduction of methoxycarbonylthiadiazole.<sup>65</sup>

### 3. Ketones

Various condensations of 3-acetyl-1,2,5-thiadiazole (**83**) have been carried out which indicate a high degree of reactivity of both the carbonyl and the methyl group. The reactions investigated include the aldol condensation of **88**, the Mannich reaction to **89**, triscyanoethylation to **90**, and the Willgerodt-Kindler reaction to **91**. The reactions proceeded under mild conditions and the normal products were obtained in good yield in each case.<sup>65</sup>

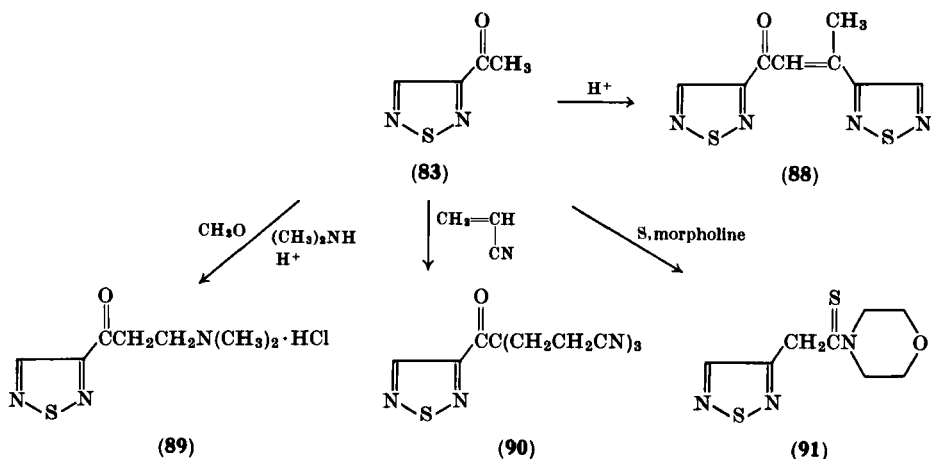
The behavior of 3-acetyl-1,2,5-thiadiazole (**87**) in several reduction reactions was also studied. The Leukart reaction produced the expected product, 1-[3-(1,2,5-thiadiazolyl)]ethylamine, but the Wolff-Kishner reaction failed to yield any ethylthiadiazole under various conditions examined. Sodium borohydride smoothly reduced both acetyl- and benzoylthiadiazole to the corresponding carbinols.

The Arndt-Eistert synthesis was investigated by Marquardt<sup>51</sup> who obtained 3-diazoacetyl-1,2,5-thiadiazole (**92**) in good yield from 3-chlorocarbonyl-1,2,5-thiadiazole (**81**) and diazomethane. When the Wolff rearrangement of **92** was carried out in the usual manner, i.e., with silver oxide as a catalyst, ring degradation resulted and none of the expected 1,2,5-thiadiazole-3-acetic acid (**93**) was isolated. By

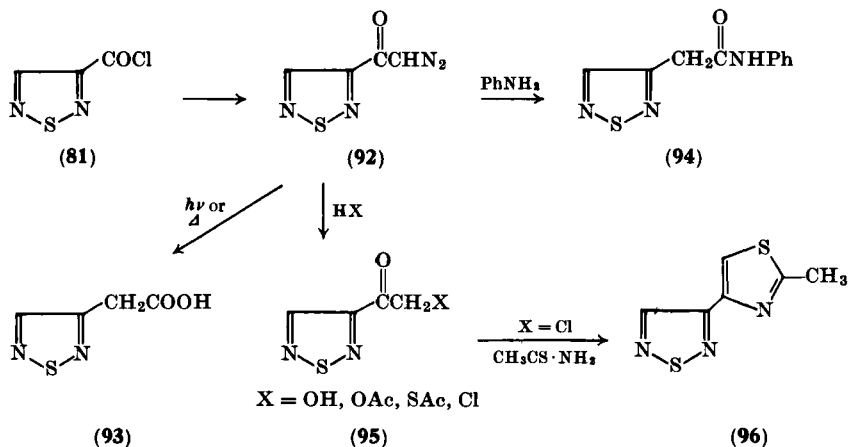
<sup>67</sup> J. Kollonitsch, *J. Chem. Soc., A., Inorg., Phys. Theoret.*, 453 (1966).

<sup>68</sup> J. Kollonitsch, *J. Chem. Soc., A., Inorg., Phys. Theoret.*, 456 (1966).





using boiling aniline alone as the reagent, rearrangement occurred and the acetanilide derivative (94) was formed. Wen<sup>16</sup> later found that the Wolff rearrangement of 92 could also be effected either by heating with dimethylaniline in benzyl alcohol or by irradiation of 92 in methanol solution. In each case, an ester of 1,2,5-thiadiazole-3-acetic acid was formed which was readily hydrolyzed to the free acid. Decarboxylation of 93 provided 3-methyl-1,2,5-thiadiazole, the first alkylthiadiazole to be synthesized.<sup>65</sup> This tedious method for obtaining methylthiadiazole is no longer required in light of the more recently

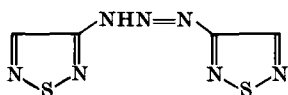


developed one-step synthesis of alkylthiadiazoles from  $\alpha$ -diamines, e.g., methylthiadiazole from 1,2-diaminopropane (Section II,B,1).

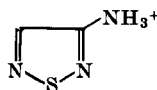
The diazoketone reacts normally with acidic reagents forming the substituted ketones (**95**, X = OH, OAc, SAc, and Cl) with sulfuric, acetic, thioacetic, and hydrochloric acids, respectively.<sup>16, 51</sup> The chloroketone was converted into the thiazole (**96**) on treatment with thioacetamide.<sup>16</sup>

#### E. AMINO- AND HYDROXY-1,2,5-THIADIAZOLES

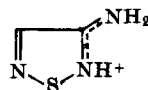
3-Amino-1,2,5-thiadiazole is, not unexpectedly, a weak base, exhibiting a  $pK_a$  in water of 2.90. The  $pK_a$  of the iso- $\pi$ -electronic compound, 2-aminopyrazine, is 3.14. Aminothiadiazole behaves normally in acylation reactions and acetyl, benzoyl, carbamoyl, and



(97)



(98)



(99)

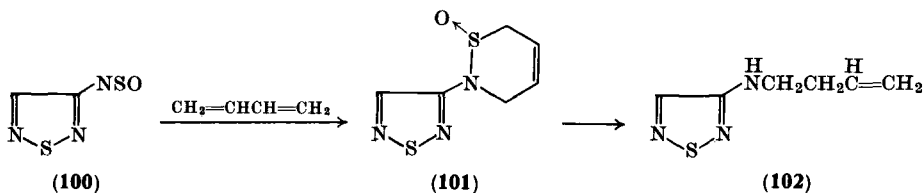
sulfanilyl derivatives have been prepared. Its behavior in diazotization in acid aqueous medium, however, is anomalous and only the diazoamino compound (**97**) formed in high yield.<sup>27</sup> Compound **97** was regarded as arising from condensation of either an *N*-nitroso intermediate or a normal diazonium salt with unreacted amine.

The spectroscopic evidence available indicates that aminothiadiazole protonates on a ring nitrogen rather than on the exo nitrogen. This property is also displayed by 2- and 4-aminopyridine. Collins<sup>27</sup> pointed out that the NH stretching absorption bands at 2775 and 2565  $\text{cm}^{-1}$  in the infrared spectrum of aminothiadiazole hydrochloride are atypical for hydrochlorides of primary amines which are usually found to absorb strongly in the frequency range 3350–3150  $\text{cm}^{-1}$ . The amine hydrochloride structure **99** was considered to be more in agreement with the observed spectrum than the structure **98**. Furthermore, the ultraviolet spectra of the protonated and unprotonated form of aminothiadiazole are identical ( $\lambda_{\text{max}}$ ; 295  $\text{m}\mu$  in water). If protonation had taken place on the exo nitrogen, as in **98**, the spectrum should be very similar to the unsubstituted ring ( $\lambda_{\text{max}}$ ; 253  $\text{m}\mu$ ).

Lastly, Gill<sup>65</sup> found that the ring proton frequency in the nuclear magnetic spectrum of aminothiadiazole is shifted upfield by +0.53 $\tau$  versus the unsubstituted compound. The  $\text{NH}_3^+$  group in **98**, however,

should decrease the electron density in the ring and show a  $-\Delta\tau$ , just opposite to the observed effect. The effect of other substituents on the ring proton frequency in 1,2,5-thiadiazoles is discussed in Section V,D.

3-*N*-Sulfinylamino-1,2,5-thiadiazole (**100**) was prepared by reaction of aminothiadiazoole with thionyl chloride.<sup>27</sup> The infrared absorption spectrum of **100** had two strong bands at 1188 and 1362  $\text{cm}^{-1}$ , typical of the absorption bands assigned the aromatic *N*-sulfinylamino compounds. The position of the lower-frequency band was found to bear a linear relationship with the  $\sigma$  constants of various substituent in the benzene ring.<sup>69</sup> Thus, *p*-dimethylamino-*N*-sulfinylaniline



absorbs at 1137  $\text{cm}^{-1}$  while *p*-nitro-*N*-sulfinylaniline absorbs at 1175  $\text{cm}^{-1}$ . Compound **100** absorbs at 1188  $\text{cm}^{-1}$ , further indicating that the 1,2,5-thiadiazole ring is a very powerful electron-withdrawing system.

Typical of *N*-sulfinylamino compounds, **100** functions as a dienophile in the Diels-Alder reaction and affords the cycloaddition product **101** on reaction with butadiene. On hydrolysis compound **101** is cleaved at the N—S bond with the resultant formation of ( $\Delta^3$ -*N*-butenyl)-3-amino-1,2,5-thiadiazole (**102**).

Hydroxy-1,2,5-thiadiazole exhibits marked acidic properties. The  $\text{pK}_a$  of the compound is 5.10, of the same order of magnitude as acetic acid.<sup>24a</sup> Alkyl substituents exert no effect on the acidity but negative substituents greatly increase the degree of ionization. It is interesting to note that a 4-ethoxy group lowers the  $\text{pK}_a$  by 0.7 units indicating that its effect on the hydroxyl group is essentially inductive (Table III).

The absence of absorption in the carbonyl region of the infrared spectra of hydroxythiadiazoles indicates that they exist essentially in the hydroxy form as opposed to the oxo form. Alkylation of

<sup>69</sup> G. Kresze and A. Maschke, *Chem. Ber.* **94**, 450 (1961).

hydroxythiadiazole proceeds normally with formation of products which absorb strongly in the alkoxide region and are transparent in the carbonyl region of the infrared spectrum.<sup>24a, 32</sup>

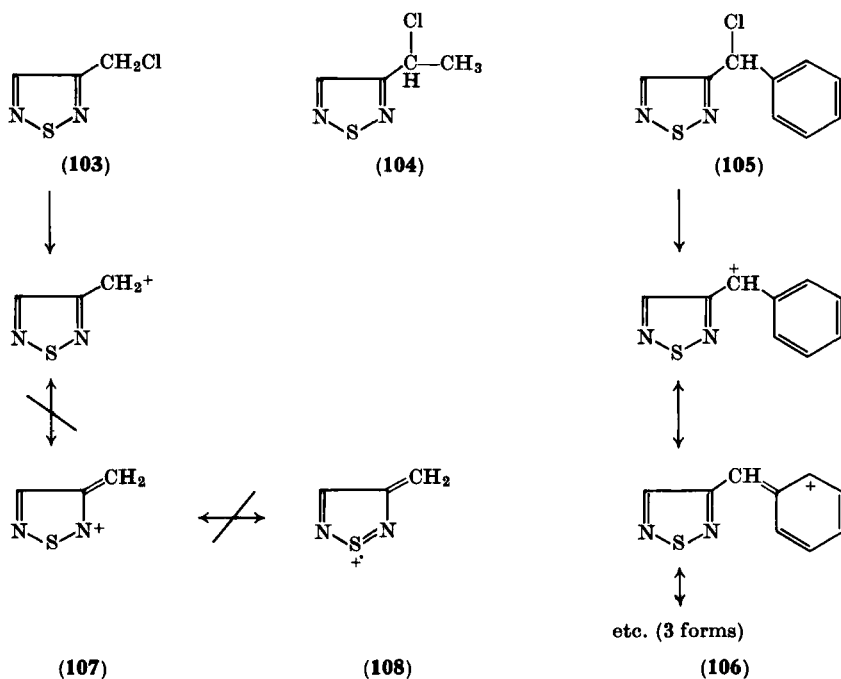
TABLE III  
pK<sub>a</sub> CONSTANTS OF 3-HYDROXY-1,2,5-  
THIADIAZOLES IN WATER

4-Substituent	pK <sub>a</sub>	Reference
H	5.10	24a
CH <sub>3</sub>	5.10	24a
CH <sub>2</sub> CH <sub>3</sub>	5.10	24a
OCH <sub>2</sub> CH <sub>3</sub>	4.40	24a
Cl	3.65	24a
CN	2.97	32
OH	4.68 (pK <sub>a2</sub> 7.50)	16

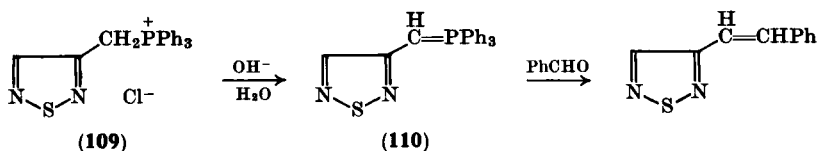
#### F. ALKYL- AND SUBSTITUTED ALKYL-1,2,5-THIADIAZOLES

The effect of the electron-withdrawing nature of the 1,2,5-thiadiazole ring on substituents containing saturated carbon atoms attached to the ring can be summarized as follows: (1) destabilization of carbonium ion; (2) stabilization of carbanions; (3) repressed S<sub>N</sub>1 reactivity; (4) enhanced S<sub>N</sub>2 reactivity. Gill<sup>65</sup> conducted a comparative study of the S<sub>N</sub>1 reactivity of the three chloroalkyl-1,2,5-thiadiazoles (**103**–**105**) by noting the rate of appearance of a silver chloride precipitate on treatment of these compounds with aqueous silver nitrate. Compounds **103** and **104**, in which the chloro groups are benzylic to the thiadiazole ring, did not produce a precipitate even after extended boiling. Compound **105**, containing a chloro group benzylic to both the thiadiazole ring and a benzene ring, gave an immediate precipitation of silver chloride even at room temperature. Thus, only in **105** is stabilization of the carbonium ion possible through resonance forms of which the net effect is donation of electron density to the α carbon. (**106**) The nonreactivity of **103** toward boiling aqueous silver nitrate is evidence against the stabilization of the carbonium ion through resonance forms like **107** and **108**; i.e., the thiadiazole ring exhibits resistance to share the electron density of its

aromatic  $\pi$  cloud. Chloromethyl-1,2,5-thiadiazole (**103**) is very reactive in  $S_N2$  reactions as evidenced by an immediate precipitate of sodium chloride on addition of **103** to sodium iodide in acetone.



The stabilization of carbanions by the 1,2,5-thiadiazole system is indicated in the facile formation of the phosphorane (**110**) by treatment of the phosphonium salt (**109**) with cold aqueous base.<sup>70</sup> The resonance-stabilized phosphorane reacts readily with aldehydes but fails to enter into a reaction with cyclohexanone.



<sup>70</sup> D. Mulvey and L. M. Weinstock, *J. Hetero. Chem.*, **4**, 445 (1967).

## IV. Biological Properties of 1,2,5-Thiadiazoles

A novel heterocyclic system such as 1,2,5-thiadiazole has considerable potential in the field of chemotherapy. Many reports of biologically active 1,2,5-thiadiazoles have appeared over the past few years and these are summarized in Table IV.

TABLE IV

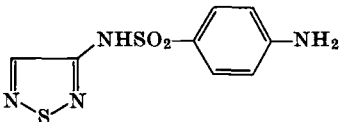
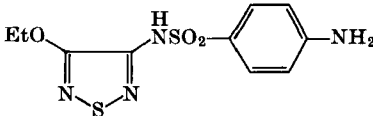
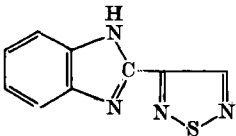
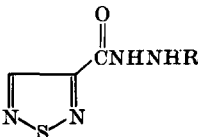
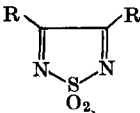
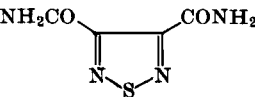
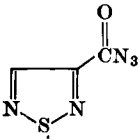
Structure	Biological activity	Reference
	Antibacterial, coccidiostat	71, 72
	Long-acting antibacterial	57, 73
	Antihelmintic	74
	Monoamine oxidase inhibitor	75
	Local antiinflammatory agents	43-45
	Antidiabetic	76

TABLE IV—*continued*

Structure	Biological activity	Reference
	Antifungal, antinematodal	64

## V. Physical and Theoretical Aspects of 1,2,5-Thiadiazoles

### A. MOLECULAR GEOMETRY

Electron diffraction data obtained by the sector microphotometer method<sup>77</sup> and data obtained by microwave spectroscopy<sup>78</sup> indicate that 1,2,5-thiadiazole is a planar pentagon of  $C_{2v}$  symmetry to within 0.1 Å. The shape of this molecule is very similar to thiophene except for a scale factor shift of 5% to shorter bond length for the thiadiazole molecule. Table V shows refined comparative data for benzene, thiophene, and 1,2,5-thiadiazole. Data for pyrazine and 1,2,5-oxadiazole are included for information. If Pauling's equation for computation of double bond character is assumed to hold<sup>79</sup> it can be seen that the  $C_1-C_2$  bond in thiophene and the  $C-N$  bond in thiadiazole both have a high degree of double bond character ( $\sim 70\%$ ). The

<sup>71</sup> M. Carmack and L. M. Weinstock, U.S. Patent 3,066,147 (1962); *Chem. Abstr.* **58**, 7949 (1963).

<sup>72</sup> K. Pfister, U.S. Patent 3,247,061 (1966).

<sup>73</sup> K. Menzl, U.S. Patent 3,213,088 (1965); see also German Patent 1,195,322; *Chem. Abstr.* **63**, 14875 (1965).

<sup>74</sup> H. D. Brown and L. H. Sarett, U.S. Patent 3,055,907 (1962); *Chem. Abstr.* **58**, 2456 (1963).

<sup>75</sup> J. M. Sprague and E. J. Cragoe, Jr., U.S. Patent 3,027,381 (1962); *Chem. Abstr.* **57**, 7280 (1962).

<sup>76</sup> M. Carmack, D. Shew, and L. M. Weinstock, U.S. Patent 2,990,408 (1961); *Chem. Abstr.* **56**, 4775 (1962).

<sup>77</sup> F. A. Momany and R. A. Bonham, *J. Am. Chem. Soc.* **83**, 4475 (1961); **86**, 162 (1964).

<sup>78</sup> S. V. Dobyns and L. Pierce, *J. Am. Chem. Soc.* **85**, 3553 (1963).

<sup>79</sup> L. Pauling, "The Nature of the Chemical Bond." Cornell Univ. Press, Ithaca, New York, 1949, p. 164.

TABLE V

STRUCTURAL PARAMETERS FOR 1,2,5-THIADIAZOLE AND RELATED COMPOUNDS

	$r_{C_1-C_2}^a$	$r_{C_2-C_3}$	$r_{S-C}$	$r_{S-N}$	$r_{C-N}$	$r_{O-N}$	$\angle N-S-N$
Benzene <sup>b</sup>	1.397	—	—	—	—	—	—
Thiophene <sup>c</sup>	1.370	1.419	1.714	—	—	—	—
1,2,5-Thiadiazole <sup>d</sup>	—	1.420	—	1.631	1.328	—	99.55°
1,2,5-Thiadiazole <sup>e</sup>	—	1.413	—	1.632	1.329	—	99.4°
Pyrazine <sup>f</sup>	—	1.39	—	—	1.35	—	—
1,2,5-Oxadiazole <sup>g</sup>	—	1.421	—	—	1.300	1.380	—

<sup>a</sup> C<sub>1</sub>—C<sub>2</sub> is the bond nearest to S in thiophene.<sup>b</sup> A. Almenningen, O. Bastiansen, and L. Fernholt, *Kgl. Norske Videnskab, Selskabs. Skrifter* 112 (1958); I. L. Karle, *J. Chem. Phys.* **20**, 65 (1952).<sup>c</sup> R. A. Bonham and F. A. Momany, *J. Phys. Chem.* **67**, 2474 (1963).<sup>d</sup> S. V. Dobyys and L. Pierce, *J. Am. Chem. Soc.* **85**, 3553 (1963).<sup>e</sup> F. A. Momany and R. A. Bonham, *J. Am. Chem. Soc.* **83**, 4475 (1961); **86**, 162 (1964).<sup>f</sup> V. Schomaker and L. Pauling, *J. Am. Chem. Soc.* **61**, 1769 (1939).<sup>g</sup> See ref. 85.

TABLE VI

BOND LENGTH [ $r_g(0)$ ] AND VIBRATION AMPLITUDES ( $l$ )  
AND THEIR CALCULATED PRECISION FOR  
1,2,5-THIADIAZOLE IN Å UNITS<sup>a</sup>

	$r_g(0)$	$\delta r$	$l$	$\delta l$
C—H	1.080	0.010	0.078	0.010
S—N	1.632	0.005	0.048	0.007
N—C	1.329	0.008	0.040 <sup>b</sup>	—
C—C	1.413	0.010	0.043 <sup>b</sup>	—
$\angle N-S-N$	99.4 ± 0.2°	—	—	—
$\angle S-N-C$	106.5 ± 0.4°	—	—	—

<sup>a</sup> F. A. Momany and R. A. Bonham, *J. Am. Chem. Soc.* **83**, 4475 (1961); **86**, 162 (1964).<sup>b</sup> Assumed values.



TABLE VII  
MOLECULAR PARAMETERS OF 1,2,5-THIADIAZOLE<sup>a</sup>

Rotational constants (Mc)			Moments of inertia (AMU-A <sup>2</sup> )			Quantum defect <sup>b</sup>	Quadrupole moments (Mc)		Dipole moment ( $\mu$ )	$\angle$ CCH
<i>A</i>	<i>B</i>	<i>C</i>	<i>I<sub>A</sub></i>	<i>I<sub>B</sub></i>	<i>I<sub>C</sub></i>		$ \chi_{AA} ^c$	$\chi_{CC} - \chi_{BB}^c$		
8538.55	6333.03	3633.97	59.2057	79.8245	139.1126	0.0824	1.0	$5.2 \pm 0.3$	$1.565 \pm 0.015$ D.	$126^\circ 14' \pm 10'$

<sup>a</sup> S. V. Dobyys and L. Pierce, *J. Am. Chem. Soc.* **85**, 3553 (1963).

<sup>b</sup> Q.D. =  $I_C - I_B - I_A$ . The Q.D. is small and similar for all isotopic species and strongly supports planarity of the molecule.

<sup>c</sup> Assignable splittings are difficult to resolve.

double bond character of the S—C and S—N bond is somewhat ambiguous, but to a first approximation both seem to have about 30% double bond character. This indicates that the substitution of two nitrogens at the 2- and 5-positions of the thiophene nucleus has little effect on the overall aromaticity of that molecule. This conclusion is compatible with closely similar bond character in the C—C bond opposite the sulfur atom in the two heterocycles, as well as with close correspondence between the bond length of this bond and the benzene C—C bond. Additional structural parameters for 1,2,5-thiadiazole are given in Table VI.

The microwave spectrum<sup>78</sup> generally supports the bond lengths, bond angles, and planar geometry indicated by electron diffraction. Pertinent data are shown in Table VII.


No x-ray diffraction data are available on 1,2,5-thiadiazole itself. McDonald<sup>80</sup> did extensive single-crystal work on 1,2,5-thiadiazole-3,4-dicarboxamide, m.p. 240°C. The compound crystallized in the triclinic system with space group *PT*, an assignment also confirmed by the absence of piezoelectric or pyroelectric effects. A trial structure was obtained by a three-dimensional sharpened Patterson synthesis using IBM 650 and 704 electronic data processing equipment. McDonald concluded that the thiadiazole ring in the molecule above in the solid state is essentially planar (estimated maximum deviation 0.0009 Å). The two carboxamide functions are also coplanar with the ring (estimated maximum deviation 0.005 Å) and an infinite number of amide hydrogen bonds interconnect the molecule in the crystal lattice. Table VIII contains the molecular dimensions obtained by McDonald for the thiadiazole ring portion of the bisamide. Comparison of these data with those reported in Table V obtained by electron diffraction and microwave spectroscopy for the unsubstituted 1,2,5-thiadiazole ring shows good agreement especially when considering the extensive stereoelectronic requirements of the vicinal carboxamide substituents.

McDonald estimated the double bond character and bond order of the thiadiazole ring bonds in the bisamide using Pauling's<sup>81</sup> and

<sup>80</sup> R. R. McDonald, Ph.D. Dissertation, Indiana University (1962); *Dissertation Abstr.* **23**, 1897 (1962).

<sup>81</sup> L. Pauling, "Nature of the Chemical Bond," 2nd ed., p. 175, Cornell Univ. Press, Ithaca, New York, 1945; 3rd ed., p. 229, Cornell Univ. Press, Ithaca, New York, 1960.

TABLE VIII  
BOND LENGTH AND BOND ANGLES OF THIADIAZOLE RING IN  
SOLID 1,2,5-THIADIAZOLE-3,4-DICARBOXAMIDE<sup>a</sup>

				
C—C	1.437 Å	—		
C—N	1.319 Å	C <sub>1</sub> —N <sub>1</sub>		
	1.325 Å	C <sub>2</sub> —N <sub>2</sub>		
S—N	1.621 Å	S—N <sub>1</sub>		
	1.619 Å	S—N <sub>2</sub>		
∠NCC	113.15°	at C <sub>1</sub>		
	112.23°	at C <sub>2</sub>		
∠SNC	107.65°	at N <sub>1</sub>		
	108.00°	at N <sub>2</sub>		
∠NSN	98.75°	—		

<sup>a</sup> R. R. McDonald, Ph.D. Dissertation, Indiana University (1962); *Dissertation Abstr.* **23**, 1897 (1962).

Gordy's<sup>82</sup> equations. The results are shown in Table IX. The S—N bond is perhaps the most interesting: its length, bond order, and double bond character agree with the S—N bond found in (SN)<sub>4</sub> by x-ray<sup>83</sup> or electron diffraction methods.<sup>84</sup>

TABLE IX  
DOUBLE BOND CHARACTER  $X$  AND BOND ORDER  $N_{A-B}$ ; IN THE  
THIADIAZOLE RING OF 1,2,5-THIADIAZOLE-3,4-DICARBOXAMIDE

A—B	Single bond length (Å)	Double bond length (Å)	$X$	$N_{A-B}$
S—N	1.74	1.56	0.40	1.40
C—N	1.47	1.29	0.54	1.54
C—C	1.54	1.33	0.50	1.50

<sup>82</sup> W. Gordy, *J. Chem. Phys.* **15**, 305 (1947).

<sup>83</sup> D. Clark, *J. Chem. Soc.*, 1615 (1952).

<sup>84</sup> C. S. Lu and J. Donohue, *J. Am. Chem. Soc.* **66**, 818 (1944).

Microwave spectroscopy on related heterocycles like 1,2,5-oxadiazole<sup>85</sup> and 1,3,4-thiadiazole<sup>86</sup> has led to an interesting ranking of these molecules in order of decreasing "aromaticity" as 1,2,5-thiadiazole > thiophene > 1,3,4-thiadiazole > 1,2,5-oxadiazole. The almost normal O—N bond distance in the oxadiazole indicates this molecule to consist essentially of an ordinary system of two conjugated double bonds without any sizable degree of aromaticity. This is further borne out by a comparison of the C—N bond lengths of the two molecules<sup>85</sup> (see Table V).

### B. ULTRAVIOLET ABSORPTION SPECTRA

The ultraviolet absorption maxima of various 1,2,5-thiadiazoles are given in Table X. In general these spectra conform in shape,

TABLE X

ULTRAVIOLET ABSORPTION MAXIMA OF 3-SUBSTITUTED 1,2,5-THIADIAZOLES

3-Substituent	Solvent	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$	Reference
H	MeOH	253	7800	8
CH <sub>3</sub>	MeOH	257–258	8600–10,000	65
Cl	MeOH	263	8630	24a
COOH and derivatives	Isopropanol	263	10,500	8, 15
CN	MeOH	263	10,000	51
Ph	Isooctane	280	13,500	40
OCH <sub>3</sub>	MeOH	272	8,560	24a
OH	MeOH	273	7,420	24a
NH <sub>2</sub>	MeOH	298	11,900	27
NHCOOR	Isopropanol	279	11,700	8
COR	MeOH	265	13,200	65

position, and intensity to spectra arising from  $\pi \rightarrow \pi^*$  transitions in five-membered heterocyclic molecules containing more than one hetero atom.<sup>87</sup> Comparison of the ultraviolet absorption spectra of

<sup>85</sup> E. Saegbarth and A. P. Cox, *J. Chem. Phys.* **43**, 166 (1965).

<sup>86</sup> B. Bak, L. Nygaard, E. J. Pedersen, and J. Rastrup-Andersen, *J. Mol. Spectry.* **19**, 283 (1966).

<sup>87</sup> S. F. Mason, *Phys. Methods Heterocyclic Chem.* **2**, 59 (1963).

1,2,5-thiadiazoles with those of their corresponding pyrazine analogs affords a good example of the parallelism between these two iso- $\pi$ -electronic systems. The data in Table XI show close similarities in

TABLE XI  
COMPARISON OF ULTRAVIOLET ABSORPTION SPECTRA OF 1,2,5-THIADIAZOLES  
AND ANALOGOUS PYRAZINES

Molecule	Solvent	$\lambda_{\max}$ (log $\epsilon$ )		Reference
		$n \rightarrow \pi^*$	$\pi \rightarrow \pi^*$	
1,2,5-Thiadiazole	H <sub>2</sub> O	—	253 (3.89) <sup>a</sup>	8
	Conc HCl	—	255 (3.89) <sup>a</sup>	8
	96% H <sub>2</sub> SO <sub>4</sub>	—	261 (3.99) <sup>a</sup>	8
	Isooctane	—	260 (3.68) <sup>a</sup>	8
			257 (3.83) 253 (3.87) 250 (3.86)	
Pyrazine	H <sub>2</sub> O	301 (2.98) <sup>a</sup>	261 (3.82) <sup>a</sup>	8
			267 (3.72)	
	Conc HCl	—	272 (3.78) <sup>a</sup>	8
	96% H <sub>2</sub> SO <sub>4</sub>	—	284 (3.88) <sup>a</sup>	8
	Isooctane	309 (2.81) <sup>a</sup> 315 (2.91) <sup>a</sup>	253 (3.72) <sup>a</sup> 260 (3.82) <sup>a</sup> 267 (3.56)	8
1,2,5-Thiadiazole-3-carboxylic acid	C <sub>6</sub> H <sub>12</sub>	328 (3.17)	260 (3.48)	87
	H <sub>2</sub> O	—	263 (4.01)	8
Pyrazine-2-carboxylic acid	H <sub>2</sub> O	310 (2.87) <sup>a</sup>	268 (3.95)	8
1,2,5-Thiadiazole-3,4-dicarboxylic acid	H <sub>2</sub> O	—	266 (3.95)	8
			222 (3.72)	
Pyrazine-2,3-dicarboxylic acid	—	—	279 (3.85)	8
1,2,5-Thiadiazole-3,4-dicarbonitrile	CH <sub>3</sub> OH	—	272 (4.0)	15
			225 (3.85)	
2,3-Dicyanopyrazine	CH <sub>3</sub> OH	—	275 (3.82)	15
			230 (4.02)	

<sup>a</sup> Assignment of transition type by P.I.P.

shape, maximal position, and extinction coefficient for the  $\pi \rightarrow \pi^*$  transitions in both molecular species. The pyrazine molecules have much better developed  $n \rightarrow \pi^*$  bands at longer wavelength. This is not surprising when one considers that formally the  $\pi$ -electron

density in a five-membered ring is 1.2 electrons per atom, while it is 1.0 for a six-membered ring. The reduced tendency of the former to promote a nonbonding electron into the  $\pi$ -electron system is therefore understandable.<sup>88</sup> The absorption spectrum of 1,2,5-thiadiazole in concentrated sulfuric acid shows a slight shift to longer wavelength. The shift in pyrazine is much more pronounced. It seems that both

TABLE XII

EFFECT OF SUBSTITUENTS AT POSITIONS STATED ON MAXIMAL WAVELENGTH IN ULTRAVIOLET SPECTRA OF 1,2,5-THIADIAZOLES, PYRIDINES, AND PYRIMIDINES

Substituent	1,2,5-Thiadiazole	$\Delta\lambda$ (m $\mu$ ) Pyridine			Pyrimidine		
	3	2	3	4	2	4	5
CH <sub>3</sub> , alkyl	4-5	5	6	-2	—	—	—
COR	8	—	—	—	—	—	—
Cl	10	5	9	—	—	—	—
CO <sub>2</sub> H	10	—	—	—	3	13	4
CN	10	8	8	18	—	—	—
Ph	27	—	—	—	—	—	—
OCH <sub>3</sub>	19	12	19	-22	21	5	—
OH	20	—	—	—	—	—	—
NH <sub>2</sub>	45	30	31	11	—	—	—
NHCOCH <sub>3</sub>	26	—	—	—	—	—	—

of these weak bases should utilize nonbonding electrons for formation of their conjugate acids. Consequently, their spectra should not change materially upon protonation.

Monosubstitution into the thiadiazole ring produces the changes in position of maximal wavelength and absorption intensity expected in the spectrum of a highly electron-deficient, conjugated system: all substituents shift the maximum to the red, but electron-donating groups have a much more pronounced bathochromic effect (Table XII). Comparison of substituent shifts with the corresponding shifts in substituted pyridines on pyrimidines shows reasonable correlation if the substituents are in the 3- or 2-position of the pyridine nucleus. In a formal sense the equivalent of both of these positions is present

<sup>88</sup> S. F. Mason, *Phys. Methods Heterocyclic Chem.* **2**, 61 (1963).

in 1,2,5-thiadiazole, while the corresponding 4-position with its inherent cross-conjugating chromophore system is absent.

### C. INFRARED AND RAMAN SPECTRA

The infrared spectra of protio- and deuterio-1,2,5-thiadiazole have been measured between 4000 and 400  $\text{cm}^{-1}$ .<sup>89</sup> These authors also obtained the Raman spectrum of the liquid. A complete assignment of

TABLE XIII  
RAMAN SPECTRUM OF LIQUID  $\text{C}_2\text{H}_2\text{N}_2\text{S}^a$

Frequency ( $\text{cm}^{-1}$ )	Intensity <sup>b</sup>	Polarization ratio <sup>c</sup>	Symmetry <sup>d</sup> species
3095	vs	p	$A_1$
3085	s	dp	$B_1$
1455	vw	dp	$B_1$
1375	m	dp	$A_1^e$
1350	m	dp	$A_1^e$
1250	m	p	$A_1$
1215	w	dp	$B_1$
1045	m	$p^f$	$A_1$
890	vw	dp	$B_1$
805	s	p	$A_1$
770	w	dp	$B_1$
685	m	p	$A_1$
520	vw	?	$B_2$

<sup>a</sup> B. Šoptrajanov and G. E. Ewing, *Spectrochim. Acta* **22**, 1417 (1966).

<sup>b</sup> vw = very weak; w = weak; m = medium; s = strong; vs = very strong.

<sup>c</sup> p = polarized; dp = depolarized.

<sup>d</sup> Assignments by P.I.P.

<sup>e</sup> The assignment is ambiguous in the 1360  $\text{cm}^{-1}$  region and one  $B_2$  and two  $A_2$  bands were not observed.

<sup>f</sup> Corrected from the authors' text (P.I.P.).

all the infrared active modes was made based on the rotational envelope contours of the gas phase spectra, the isotope shifts, and the polarization measurements of the Raman spectrum. The  $C_{2v}$  symmetry of the molecule classifies the fifteen normal modes into four symmetry species, one of which ( $A_2$ ) is infrared-forbidden, but Raman-allowed.

<sup>89</sup> B. Šoptrajanov and G. E. Ewing, *Spectrochim. Acta* **22**, 1417 (1966).

The two modes belonging to this species were not detected. On the other hand all six expected C—H modes were identified. The consistency of the assignment was checked by the use of the Redlich-Teller product rule which was satisfied to 0.8%.<sup>90</sup> The reported Raman spectrum is reproduced in Table XIII. There follows the reported assignment of the fundamental infrared frequencies of 1,2,5-thiadiazole in the vapor (Table XIV). The assignments above

TABLE XIV  
FUNDAMENTAL INFRARED FREQUENCIES OF C<sub>2</sub>H<sub>2</sub>N<sub>2</sub>S and C<sub>2</sub>D<sub>2</sub>N<sub>2</sub>S  
IN THE VAPOR<sup>a</sup>

Symmetry species	No.	C <sub>2</sub> H <sub>2</sub> N <sub>2</sub> S	C <sub>2</sub> D <sub>2</sub> N <sub>2</sub> S	R <sup>b</sup>	Approximate description
A <sub>1</sub>	1	3106	2318	1.340	C—H stretching
	2	1350	1294	1.043	Ring stretching
	3	1251	1183	1.057	Ring stretching
	4	1041	849	1.226	C—H in-plane bending
	5	806	753	1.070	Ring in-plane bending
	6	688	681	1.010	Ring in-plane bending
A <sub>2</sub>	7	(908) <sup>c</sup>	(735) <sup>c</sup>	—	C—H out-of-plane bending
	8	(500) <sup>c</sup>	(450) <sup>c</sup>	—	Ring out-of-plane bending
B <sub>1</sub>	9	3108	2320	1.339	C—H stretching
	10	1461	1417	1.031	Ring stretching
	11	1227	968	1.267	C—H in plane bending
	12	895	869	1.029	Ring in-plane bending
	13	780	751	1.039	Ring in-plane bending
B <sub>2</sub>	14	838	650	1.289	C—H out-of-plane bending
	15	520	506	1.028	Ring out-of-plane bending

<sup>a</sup> B. Šoptrajanov and G. E. Ewing, *Spectrochim. Acta* **22**, 1417 (1966).

<sup>b</sup> R = ratio of protonated to deuterated frequency.

<sup>c</sup> Nonobserved frequencies.

supersede earlier empirical assignments.<sup>8, 15, 51</sup> The major difference is the assignment of a characteristic band around 840 cm<sup>-1</sup> to a C—H out-of-plane bending mode, which was assigned by the earlier investigators to a mode involving vibration of the ring. Šoptrajanov's

<sup>90</sup> J. C. D. Brand and J. C. Speakman, "Molecular Structure, the Physical Approach," pp. 194 and 284. Arnold, London, 1960.



assignments correspond qualitatively to assignments reported for isomeric thiadiazoles.<sup>91</sup>

The infrared spectra of substituents attached to the 1,2,5-thiadiazole nucleus are normal for functionality attached to a strongly electron-withdrawing molecule. Existing data are presented in Table XV. A speculative insight into the electron-withdrawing power of the

TABLE XV  
INFRARED FREQUENCIES FOR SUBSTITUENTS ATTACHED TO THE  
3-POSITION OF 1,2,5-THIADIAZOLE

3-Substituent	System	$\nu$ (cm <sup>-1</sup> )	Assignment	Reference
H	Liq. film	3100	C—H	8
CO <sub>2</sub> H	KBr	1710	C=O	8
CONH <sub>2</sub>	KBr	1680	C=O	8
CONHNH <sub>2</sub>	KBr	1692	C=O	8, 27
CON <sub>3</sub>	KBr	1696	C=O	8
CO <sub>2</sub> Me	Liq. film	1720, 1740	C=O	8
CO <sub>2</sub> Et	Liq. film	1735, 1755	C=O	8, 27
CO <sub>2</sub> CH <sub>2</sub> Ph	KBr	1727, 1757	C=O	27
NHCO <sub>2</sub> Et	KBr	1750	C=O	8
COCH <sub>3</sub>	KBr	1695	C=O	65
COPh	KBr	1655	C=O	27, 65
CHO	Liq. film	1695	C=O	65
COCH <sub>2</sub> Ph	Liq. film	1695	C=O	65
CN	Liq. film	2221	C—N	51
COCHN <sub>2</sub>	KBr	1632	C=O	51
OH	KBr	3106	O—H	27
OCH <sub>3</sub>	Liq. film	1200	C—O—C	16
NH <sub>2</sub>	Liq. film	3484	N—H	27
NHCOCH <sub>3</sub>	KBr	3236	N—H	27
NSO	KBr	1180, 1362	NSO	27
NHR	Liq. film	3390	N—H	27

1,2,5-thiadiazole nucleus can be obtained by examining the variation of the infrared absorption bands assigned to thionyl anilines as a function of the characteristics of *m* and *p* substituents in benzene: A plot of  $\nu(\text{substituent}) - \nu(\text{H})$  versus Hammett's  $\sigma$  is approximately linear.<sup>69</sup> Using Kresze's formula one calculates a " $\sigma$ " for the 1,2,5-

<sup>91</sup> A. R. Katritzky and A. P. Ambler, *Phys. Methods Heterocyclic Chem.* **2**, 231 (1963) (especially Tables 27, 28 and 29).

thiadiazolyl moiety of  $\sim +1$  which is 35–25% more electron-withdrawing than *m*- or *p*-NO<sub>2</sub> substituents in molecules not involving resonance forms of the *p*-NO<sub>2</sub>-phenol or *p*-NO<sub>2</sub>-aniline type. Kresze apparently quite properly believes that such resonance contributions are unlikely in the —NSO group.<sup>92</sup>

#### D. PROTON MAGNETIC RESONANCE SPECTRA

The proton magnetic frequencies of relevant protons in 1,2,5-thiadiazole and other aromatic ring systems of interest are shown in Table XVI. The highly deshielding nature of the electron-deficient

TABLE XVI  
PROTON MAGNETIC RESONANCE FREQUENCIES OF  
1,2,5-THIADIAZOLE AND RELATED SYSTEMS

Compound	Solvent	$\tau^H$
1,2,5-Thiadiazole	CCl <sub>4</sub>	1.30 <sup>a</sup>
1,2,5-Oxadiazole	CCl <sub>4</sub>	1.34 <sup>b</sup>
Pyrazine	CCl <sub>4</sub>	1.40 <sup>a</sup>
Benzene	CDCl <sub>3</sub>	2.63 <sup>c</sup>
Pyridine	CDCl <sub>3</sub>	H <sub>2</sub> 1.40 <sup>c</sup>
		H <sub>3</sub> ca. 3.00
		H <sub>4</sub> ca. 2.40
Thiophene	CDCl <sub>3</sub>	H <sub>2</sub> 2.70 <sup>c</sup> } complex
		H <sub>3</sub> 2.90 }
Thiazole	CDCl <sub>3</sub>	H <sub>2</sub> 1.16 <sup>c</sup>
		H <sub>4</sub> 2.03
		H <sub>5</sub> 2.59
Furan	CDCl <sub>3</sub>	H <sub>2</sub> 2.58 (triplet) <sup>c</sup>
		H <sub>3</sub> 3.63 (triplet) <sup>c</sup>

<sup>a</sup> J. M. Gill, Ph.D. Dissertation, Indiana University (1963); *Dissertation Abstr.* **24**, 2690 (1964).

<sup>b</sup> R. A. Olofson and J. S. Michelman, *J. Org. Chem.* **30**, 1854 (1965).

<sup>c</sup> N. S. Bhacca, D. P. Hollis, L. F. Johnson, E. A. Pier, and J. N. Shoolery, "NMR Spectra Catalog," Combined Vols. 1 and 2. Varian Assoc., Palo Alto, California, 1963.

<sup>92</sup> L. P. Hammett, "Physical Organic Chemistry," Chapter VII. McGraw-Hill, New York, 1940.

TABLE XVII  
THE EFFECT OF SUBSTITUTION ON THE PROTON FREQUENCY OF 1,2,5-THIA DIAZOLE

Types of substituents and compounds	$\tau$	$\Delta\tau$	$\Delta\tau^a$ ( <i>o</i> -benzene)	Reference
Electron-withdrawing substituents				
1,2,5-Thiadiazole-3-carboxylic acid	0.85	-0.45	-0.63	65
1,2,5-Thiadiazole-3-carboxaldehyde	0.90	-0.40	-0.73	65
3-Acetyl-1,2,5-thiadiazole	0.95	-0.35	-0.63	65
3-Methoxycarbonyl-1,2,5-thiadiazole	0.94	-0.56	-0.93	65
3-Chlorocarbonyl-1,2,5-thiadiazole	0.78	-0.52	-0.90	65
Substituents with small inductive effect				
3-Hydroxymethyl-1,2,5-thiadiazole	1.27	-0.03	+0.07	65
3-Chloromethyl-1,2,5-thiadiazole	1.35	$\pm 0.05$	0.0	65
3-Methyl-1,2,5-thiadiazole	1.60	+0.30	+0.10	65
1,2,5-Thiadiazole-3-acetic acid	1.45	+0.15	—	65
3-Phenyl-1,2,5-thiadiazole	1.23	-0.07	—	40
Electron donors				
3-Hydroxy-1,2,5-thiadiazole	1.95	+0.65	+0.37	65
3-Amino-1,2,5-thiadiazole	2.23	+0.93	+0.77	65
3-Methoxy-1,2,5-thiadiazole	2.00	+0.70	+0.23	62

<sup>a</sup> P. L. Corio and B. P. Dailey, *J. Am. Chem. Soc.* **78**, 3043 (1956).

1,2,5-thiadiazole nucleus is apparent. It is, however, clearly matched by the analogous oxygen system, as well as by the pyrazine ring. The same relationships, albeit at higher fields, are to be observed between the chemical shifts reported for furan and thiophene. These facts represent convincing evidence that aromaticity as expressed in terms of resonance energies is not relatable to chemical shift values observed in these molecules. The same conclusion has been reached by Abraham and Thomas,<sup>93</sup> who maintain that the presence of excess magnetic anisotropy is a useful criterion for the assignment of aromaticity to a molecule, but that, again, the magnitude of this effect cannot be related to the degree of aromaticity expressed as resonance energy.<sup>94</sup> This is so, independent of the argument whether these excess magnetic anisotropies are defined as ring currents,<sup>95</sup> or by empirically estimated anisotropic Pascal's constants associated with aromatic ring atoms without distinction between  $\sigma$  and  $\pi$ -electrons.<sup>96</sup> Substituents on the 1,2,5-thiadiazole nucleus affect the remaining proton in the expected manner as shown in Table XVII. Comparison with related shifts in *o*-substituted benzenes shows again the electron deficiency of the 1,2,5-thiadiazole ring itself, since electron-withdrawing substituents are about half as effective in polarizing the electron configuration of 1,2,5-thiadiazole as in benzene, while the reverse is true for electron-donating substituents.<sup>95, 96a</sup>

Recently, Laszlo<sup>97</sup> has examined the  $^1J_{CH}$  coupling constant in cyclic molecules as a function of the endocyclic angle at C and the ionic perturbation due to a hetero atom adjacent to C. The data show that in a series of nitrogen-containing heterocycles the ionic contribution of the nitrogen atom is constant (23 cycles) and thus related to the  $\sigma$  electronegativity. This circumstance permits the calculation of  $^1J_{CH}$  values in heterocycles containing S and N. The calculated values for thiazoles, 1,2,5-oxadiazoles, and 1,2,5-thiadiazoles agree with the experimentally determined  $^1J_{CH}$  values to within 2%.

<sup>93</sup> R. J. Abraham and W. A. Thomas, *J. Chem. Soc., B, Phys. Org.*, 127 (1966).

<sup>94</sup> J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

<sup>95</sup> L. Salem, "The Molecular Orbital Theory of Conjugated Systems," p. 178 ff. Benjamin, New York, 1966.

<sup>96</sup> J. I. Musher, *J. Chem. Phys.* **43**, 4081 (1965).

<sup>96a</sup> P. L. Corio and B. P. Dailey, *J. Am. Chem. Soc.* **78**, 3043 (1956).

<sup>97</sup> P. Laszlo, *Bull. Soc. Chim. France*, 558 (1966).

## E. ELECTRONIC STRUCTURE AND BONDING

Thiadiazoles are of theoretical interest because as a class they are in a formal sense iso- $\pi$ -electronic with thiophene, thiazoles, and five-membered cyclic mono- and diazines. At the same time they are related by physical and chemical similarity to those six-membered cyclic diazines which contain an ethylenic grouping in place of the sulfur atom. 1,2,5-Thiadiazole is thus related to thiophene, isothiazole, imidazole, and pyrazine. It is therefore not surprising that the thiadiazoles have been assigned to the broad class of aromatic structures.

Aromaticity is a term which requires careful definition in terms of thermodynamic, kinetic, and mechanistic criteria.<sup>98, 99</sup> For the purpose of this review it is defined as an additional stabilization of a molecule specifically associated with delocalization of  $\pi$  electrons contained in a closed molecular orbital shell. The determination of this specific stabilization or resonance energy may be carried out experimentally or theoretically. Table XVIII contains a number of experimentally accessible parameters and their theoretical counterparts which have all been used to arrive at its value.

General reviews of these topics, their definitions and significance, are available.<sup>95, 98</sup> Their specific relevance to heterocyclic systems is extensively discussed in two monographs.<sup>99, 100</sup> It becomes instructive to examine 1,2,5-thiadiazole in the light of these guide lines. The experimental physical data, the molecular geometry, the proton magnetic spectrum, the electronic vibrational and rotational spectral data, and the mass spectrum are compatible with the hypothesis that 1,2,5-thiadiazole is an aromatic system.

The same can be said considering its chemical reactivity. The 1,2,5-thiadiazole ring is relatively stable toward oxidation. It is unreactive in electrophilic reactions or reactions which require it to acquire a positive charge in intermediates or transition states; but when appropriately substituted, the ring will undergo classical substitutions. In consequence of its electron-deficient nature, all acidic functions of the molecule are enhanced, whether they are the  $pK_a$ 's of the carboxylic acids or phenols or refer to the pronounced tendency of the unsubstituted ring to lose a proton to form its con-

<sup>98</sup> A. Streitwieser, Jr., "Molecular Orbital Theory," Chapter X. Wiley, New York, 1961.

<sup>99</sup> R. Zahradník, *Advan. Heterocyclic Chem.* **5**, 55 (1965).

<sup>100</sup> J. Ridd, *Phys. Methods Heterocyclic Chem.* **1**, 109 (1963).

jugate base. Conversely, the ring is highly electrophilic: it is prone to undergo nucleophilic substitution and is unstable towards reduction. All its basic properties are reduced, whether in form of the very low  $pK_a$  of its own conjugate acid or that of the appropriate amine.

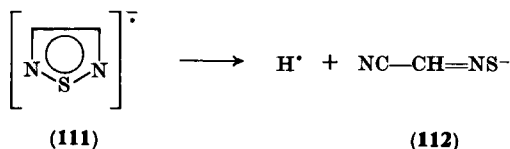
The stability toward oxidation accords well with classical concepts of aromaticity. On the other hand, the instability toward reducing agents does not. It is pointed out, however, that arguments based on

TABLE XVIII

Experimental parameter	Pertaining to	Theoretical counterpart
Heat of formation	Resonance energy in isolated molecule in ground state	MO—energy level schemes
Heat of hydrogenation		Delocalization energy
Molecular geometry	Electron distribution in isolated molecule in ground state	Bond order
Bond length		$\pi$ -bond character
Bond angles		$\pi$ -electron densities
Proton magnetic resonance	"Aromatic" magnetic susceptibility in isolated molecule in ground state ("ring current")	Free valence index
		MO—calculations of magnetic susceptibility
Reactivity toward nucleophiles, radicals, electrophiles	Energetics of molecule in transition state Energy of activation	Reactivity indices: Frontier electron density
		Localization energy $\pi$ -electron or charge density
Absorption spectra	Polarizability and symmetry of the molecule Energy level schemes	Calculation of spectra (maxima and intensities)

difference in reactivity are only meaningful in closely analogous systems where the available pathways to products are similar. Addition of electrons to aromatic systems occurs into the lowest unoccupied molecular orbital which is either anti- or nonbonding. In zeroth-order MO theory this disturbs the basic aromatic  $\pi$ -electron system only as a minor perturbation. In hydrocarbons electron addition reactions are usually reversible since no adequate pathway to other reasonable

products exist.<sup>101</sup> In the case of 1,2,5-thiadiazole, however, the initial radical anion (111) can form an open-chain sulfiminonitrile (112) with expulsion of a hydrogen atom and irreversible fission of the ring.<sup>102</sup> It is therefore not surprising that polarographic reduction of 1,2,5-thiadiazole proceeds irreversibly with the uptake of six electrons without any indication of an intermediate of finite lifetime.<sup>8</sup>



In summary, it is found that most available experimental facts support the assignment of aromatic character to 1,2,5-thiadiazole. Those facts, which at first seem to contradict the assignment, can be explained without undue difficulty. However, all these arguments are at best able to afford qualitative indications of aromaticity. Neither thermodynamic data nor a meaningful "nonaromatic" reference model is available for this molecule to establish its aromatic character in the accepted empirical and more quantitative manner.

There remains to explore whether results of theoretical calculations can shed some light on this problem. A general review<sup>99</sup> and specific papers dealing with MO-LCAO calculations of isomeric thiadiazoles<sup>103, 104</sup> illustrate at the same time the beauty and frustration of this approach. Obviously the mathematical apparatus is available to obtain approximate, but significant information. The immediate results of such calculations, the MO orbital energies, appear in terms of two basic parameters. These are, first, the Coulomb integrals ( $\alpha$ ) which specify the effective electronegativity relative to carbon of hetero atoms in conjugated cyclic systems, and, second, the resonance integrals ( $\beta$ ) which deal with the amount of bond overlap between these atoms and their neighbors. Neither of these parameters is known. It is customary to carry out the calculations varying them

<sup>101</sup> A. Streitwieser, Jr., "Molecular Orbital Theory," p. 175. Wiley, New York, 1961.

<sup>102</sup> For analogous reasoning see R. Zahradník, *Advan. Heterocyclic Chem.* **5**, 56 (1965).

<sup>103</sup> R. Zahradník and J. Koutecký, *Collection Czech. Chem. Commun.* **26**, 156 (1961).

<sup>104</sup> N. K. Ray and P. T. Nanasimhan, *Theoret. Chim. Acta* **5**, 401 (1966).

incrementally in a hopefully sensible and consistent manner. All additional results of the calculations, the total  $\pi$ -electron energies, the delocalization energies, spectroscopic transition energies, the various reactivity indices, bond order, magnetic properties, and so on, are derived from the same sets of  $\alpha$ 's and  $\beta$ 's. In a series of closely related homologs one obtains thus valuable and often semiquantitative correlations as is demonstrated in Zahradník's work on isomeric thiadiazoles.<sup>103</sup> But the disappointing fact remains that in their present state of development these calculations do not permit the assignment of aromaticity as defined above to these molecules in either relative or absolute terms. Their value is therefore no more quantitative or significant than the traditional intuition of the organic chemist.

Present theory is not even sufficiently developed to permit a decision concerning the electronic structure of the sulfur atom in heteroaromatic systems. Sulfur, belonging to the second row of the periodic table of elements, has  $3p$  and  $3d$  orbitals whose energy levels are relatively close. In interaction with other  $p$  orbitals, it can in principle form  $\pi$ -type bonding involving only its  $3p$  orbitals. On the other hand it can form a new set of three  $pd^2$  hybrid orbitals. Two of these latter orbitals are bonding and have symmetry properties which allow for effective participation in  $\pi$ -bonding of a  $p$ - $pd$  type with concomitant expansion of the  $(3s)^2(3p)^6$  valence shell of the atom.<sup>105</sup> This ability of sulfur to participate in two distinct types of  $\pi$  bonding is well-documented.<sup>106-108</sup> The question of which of the two electronic structures obtains for sulfur in heterocyclic systems, and whether it is always the same, has by no means been settled, although a preponderance of recent papers seems to favor involvement of the  $3d$  orbitals.<sup>109-112</sup> It has been proposed<sup>99</sup> that the availability and participation of  $pd$  hybrid orbitals is responsible for the higher resonance

<sup>105</sup> H. C. Longuet-Higgins, *Trans. Faraday Soc.* **45**, 173 (1949).

<sup>106</sup> C. C. Price and S. Oae, "Sulfur Bonding." Ronald Press, New York, 1962.

<sup>107</sup> D. J. Cram, "Fundamentals of Carbanion Chemistry," p. 71 ff. Academic Press, New York, 1965.

<sup>108</sup> G. Cilento, *Chem. Rev.* **60**, 147 (1960).

<sup>109</sup> L. Salem, "The Molecular Orbital Theory of Conjugated Systems," p. 158 ff. Benjamin, New York, 1966.

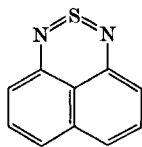
<sup>110</sup> D. P. Craig, *Theoret. Org. Chem. Papers Kekule Symp. London*, 1958 p. 20. Butterworth, London and Washington, D.C., 1959.

<sup>111</sup> N. L. Paddock, *Quart. Rev. (London)* **18**, 168 (1964).

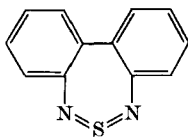
<sup>112</sup> W. H. Poesche, *J. Chem. Soc., B, Phys. Org.*, 568 (1966).



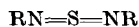
energies of thioheterocycles when compared with their N or O analogs. The sulfur systems are thus not only iso- $\pi$ -electronic with benzene, which is equally true for the five-membered oxo or aza systems, but they have the same ratio of  $\pi$ -electrons to orbitals, which on this basis is 1.0 for benzene and thiophene, but 1.2 for furan and pyrrole. The sulfur atoms in these rings have two participating orbitals per atom, a condition which does not violate any laws of quantum mechanics as long as spatial and symmetry requirements for bonding are satisfied.



(113)



(114)



(115)

In our view, it is this circumstance which accounts for the chemical and physical similarities between thiophene and benzene, as well as between pyrazine and 1,2,5-thiadiazole, which have frequently been pointed out in this review and in the chemical literature.<sup>113</sup> In a formal sense the sulfur atom having two *pd* orbitals is like an ethylenic fragment with two *p* orbitals. We therefore propose that a sulfur-containing heterocycle be termed quasiethylenic with its cyclic counterpart in which the sulfur atom is replaced by two doubly bonded carbon atoms.

The question can be raised whether the  $\text{—N}=\text{S}=\text{N—}$  grouping gives particular stability to the 1,2,5-thiadiazoles rather than the delocalization of the equivalent of six  $\pi$  electrons. Experimental evidence indicates that the latter is true. Molecules which contain this  $\text{—N}=\text{S}=\text{N—}$  arrangement of atoms in six- and seven-membered rings (113 and 114), which formally do not belong to the  $(4n+2)$  Hückel series, show very little stability and are easily decomposed by water<sup>114</sup> or on heating.<sup>27</sup> In such systems, a relatively stable cation can be predicted by analogy to the tropylium ion. Equally unstable are the ylidlike sulfur diimides (115), which contain the NSN triad in

<sup>113</sup> V. Bogert-Schatz, in "Medicinal Chemistry" (A. Burger, ed.), 2nd ed., p. 78 and 79 ff. Wiley (Interscience), New York, 1960.

<sup>114</sup> R. Dietz, *Chem. Commun.* p. 57 (1965); H. Behringer and K. Leiritz, *Chem. Ber.* **98**, 3196 (1965).

open-chain form.<sup>115, 116</sup> The stability of these molecules is increased by neighboring conjugation.<sup>117</sup> The chemistry of sulfur diimides has been the subject of a recent extensive review.<sup>117a</sup>

Tetrasulfur tetranitride ( $S_4N_4$ ) also contains N—S—N atom arrangements. Its structure has been a subject of controversy for many years, but current interpretation of chemical and physical reactivity as well as theoretical calculations indicate a cyclic structure with delocalized  $\pi$  electrons involving  $pd$  hybrid orbitals on sulfur.<sup>118</sup> Such a structural assignment leads formally to a ring with twelve  $\pi$  electrons, again not a member of the  $(4n + 2)$  Hückel set. Whether the Hückel rules have the same significance in these types of structures can be questioned, especially when the less stringent geometrical requirements of  $p$ - $pd$  orbital overlap are considered. But in any case,  $S_4N_4$  is not very stable chemically and is prone to form a series of anions. Extended Hückel MO calculations handle this situation quite well: twenty-two MO levels are occupied by the 44  $s$  and  $p$  electrons of all atoms involved and the first empty level is fourfold degenerate, affording ample space for anion formation.<sup>119</sup>

<sup>115</sup> M. Goehring and G. Weis, *Angew. Chem.* **68**, 678 (1956).

<sup>116</sup> D. H. Clemens, A. J. Bell, and J. L. O'Brien, *Tetrahedron Letters*, 1487, 1491 (1965).

<sup>117</sup> J. Hancock and A. R. Markert, *Tetrahedron Letters*, 6157 (1966).

<sup>117a</sup> G. Kresze and W. Wucherpfennig, *Angew. Chem.* **79**, 124 (1967).

<sup>118</sup> C. W. Allen, *J. Chem. Educ.* **44**, 38 (1967).

<sup>119</sup> A. G. Turner and F. S. Mortimer, *Inorg. Chem.* **5**, 906 (1966).

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# Recent Advances in the Chemistry of 1,3,4-Thiadiazoles

JAN SANDSTRÖM

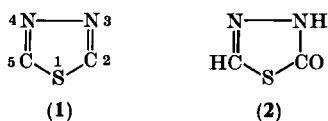
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## I. Introduction

The development of 1,3,4-thiadiazole chemistry is linked to the discovery of phenylhydrazine by Emil Fischer and of hydrazine by Th. Curtius in the late nineteenth century. The first 1,3,4-thiadiazole was described by Fischer in 1882, but the true nature of the ring system was demonstrated first in 1890 by Freund and Kuh. From 1894 Busch and his school took up work in this field, and they came to play a leading part in the rapid expansion during the first decades of the twentieth century. After a period of relatively low activity between the wars, interest was renewed due to the discovery of sulfa drugs

and of potent representatives in the thiadiazole series. The pharmaceutical line of interest has continued, and new interesting drugs have been discovered. This development has considerably enriched the preparative side of 1,3,4-thiadiazole chemistry. During the last decade, several research groups have been attracted by the diverse tautomerism possibilities in amino-, hydroxy-, and mercapto-1,3,4-thiadiazoles, and this has led to the collection of much new information on the physical properties of these compounds.



The field has been surveyed in two review articles,<sup>1, 2</sup> the latter covering the literature up to 1956. The present review will therefore mainly be concerned with results published during the last decade. The literature has been covered up to the end of 1966 with some additions from 1967.

The numbering of the 1,3,4-thiadiazole ring follows from **1**. Clockwise or anticlockwise numbering is used according to convenience. In 2- or 5-imino-, -oxo-, or -thiono-1,3,4-thiadiazoles, the position of the "extra" hydrogen atom is shown by the corresponding number in parentheses, e.g., 1,3,4-thiadiazolin-2(3)-one (**2**).

## II. 1,3,4-Thiadiazole and Its Homologs

### A. THE PARENT COMPOUND, ITS ALKYL AND ARYL DERIVATIVES

The unsubstituted 1,3,4-thiadiazole (**3**, R = H) was described in 1956 by Goerdeler *et al.*<sup>3</sup> They transformed 2-amino-1,3,4-thiadiazole (**4**, R = H) into the 2-bromo compound (**5**, R = H) by a Sandmeyer reaction, and by hydrogenation of the latter with Adams catalyst the parent compound of the series was obtained as a colorless solid, m.p. 42–43°, b.p. 204–205°. Jensen and Pedersen<sup>4</sup> prepared the same

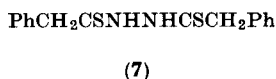
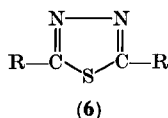
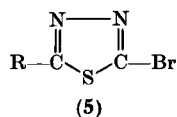
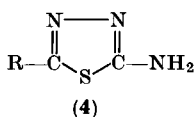
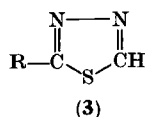
<sup>1</sup> L. L. Bambas, "Five-Membered Heterocyclic Compounds," p. 81. Wiley (Interscience), New York, 1952.

<sup>2</sup> W. R. Sherman, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, p. 587. Wiley, New York, 1961.

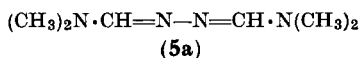
<sup>3</sup> J. Goerdeler, J. Ohm, and O. Tegtmeier, *Chem. Ber.* **89**, 1534 (1956).

<sup>4</sup> K. A. Jensen and C. Pedersen, *Acta Chem. Scand.* **15**, 1124 (1961).

compound by bisthioformylation of hydrazine with sodium dithioformate, followed by spontaneous cyclization. By the Goerdeler and Jensen methods, four differently isotopically substituted 1,3,4-thiadiazoles were prepared for microwave studies.<sup>5</sup> A method suitable for preparation of 1,3,4-thiadiazoles in larger quantities has recently been described by Föhlich *et al.*<sup>5a</sup> *N,N*-Dimethylformamide and



*N,N'*-diformylhydrazine condense in the presence of phosgene to the hydrochloride of *N,N*-dimethylformamide-azine (5a), the free base



of which reacts with hydrogen sulfide in methanol to give 1,3,4-thiadiazole in 80 % yield. 2-Methyl-1,3,4-thiadiazole (3, R = CH<sub>3</sub>) was prepared analogously with the parent compound.<sup>3</sup> Several 2,5-dialkyl-1,3,4-thiadiazoles are known from the classical work of Stollé and collaborators.<sup>6, 7</sup> They were generally prepared by reaction between 1,2-diacylhydrazines and phosphorus pentasulfide. 2,5-Dibenzyl-1,3,4-thiadiazole (6, R = PhCH<sub>2</sub>) was formed from phenylthioacetylhydrazide on storing at room temperature, probably with 1,2-bisphenylthioacetylhydrazine (7) as an unstable intermediate.<sup>4</sup>

<sup>5</sup> B. Bak, C. H. Christensen, T. S. Hansen, E. J. Pedersen, and J. T. Nielsen, *Acta Chem. Scand.* **19**, 2434 (1965).

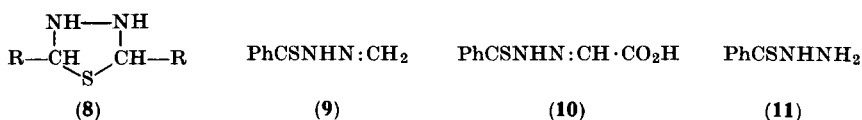
<sup>5a</sup> B. Föhlich, R. Brann and K. W. Schultze, *Angew. Chem.* **79**, 318 (1967).

<sup>6</sup> R. Stollé, *Ber.* **32**, 797 (1899).

<sup>7</sup> R. Stollé and H. Hille, *J. Prakt. Chem.* [2] **69**, 481 (1904).

Thioacylation of thiohydrazides, preferably with carboxymethyl dithioates, has been demonstrated as a general method for the preparation of 2,5-dialkyl- or 2,5-diaryl-1,3,4-thiadiazoles.<sup>4</sup> The intermediate 1,2-bisthioacylhydrazines in most cases are too unstable to be isolated.

Rühlmann<sup>8</sup> prepared 2,5-dialkyl-1,3,4-thiadiazoles (**6**) in high yields via 1,3,4-thiadiazolidines (**8**). These were obtained from hydrazine, hydrogen sulfide, and aliphatic aldehydes, and they were oxidized to **6** by sulfur in boiling piperidine.



2-Phenyl-1,3,4-thiadiazole (**3**, R = Ph) was first prepared by Ohta *et al.*<sup>9</sup> by thioformylation of benzhydrazide with sodium dithioformate, followed by dehydrating cyclization in sulfuric acid. In the same way the 2-benzyl and some aromatic analogs were obtained. Holmberg<sup>10</sup> prepared **3** (R = Ph) by oxidation of 1-methylene-2-thiobenzoylhydrazine (**9**) and of glyoxylic acid thiobenzhydrazone (**10**) with ferric chloride, and finally by reaction between thiobenzhydrazide (**11**) and formic acid.

**3** (R = Ph) is also formed in the reaction between diazomethane and thiobenzoyl chloride,<sup>11</sup> probably via a 1,3-dipolar addition of diazomethane to the thiocarbonyl group. Similar additions have been observed by Huisgen *et al.*<sup>12</sup> The reaction between thioacyl chlorides and diazo compounds was first studied by Staudinger and Siegwart.<sup>13</sup> **3** (R = Ph) has been prepared by cyclization of **11** with triethylorthoformate,<sup>14</sup> and also from 2-phenyl-1,3,4-oxadiazole and phosphorus pentasulfide.<sup>15</sup>

<sup>8</sup> K. Rühlmann, *J. Prakt. Chem.* [4] **8**, 285 (1959).

<sup>9</sup> M. Ohta, R. Hagiwara, and Y. Mizushima, *J. Pharm. Soc. Japan* **73**, 701 (1953); *Chem. Abstr.* **48**, 7005 (1954).

<sup>10</sup> B. Holmberg, *Arkiv Kemi*, **9**, 65 (1955).

<sup>11</sup> T. Bacchetti and A. Alemagna, *Rend. Ist. Lombardo Sci. Pt. I* **91**, 617 (1957).

<sup>12</sup> R. Huisgen, R. Greshey, M. Seidel, H. Knupfer, and R. Schmidt, *Ann. Chem.* **658**, 169 (1962).

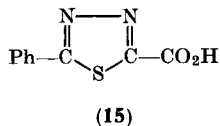
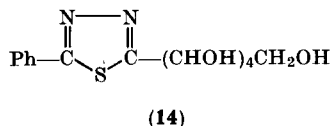
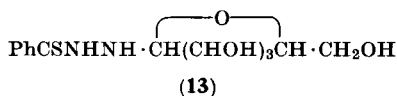
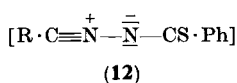
<sup>13</sup> H. Staudinger and J. Siegwart, *Helv. Chim. Acta* **3**, 840 (1920).

<sup>14</sup> C. Ainsworth, *J. Am. Chem. Soc.* **77**, 1150 (1955).

<sup>15</sup> C. Ainsworth, *J. Am. Chem. Soc.* **80**, 5201 (1958).

2-Alkyl-5-aryl- and 2,5-diaryl-1,3,4-thiadiazoles were prepared by cyclization of **11** with ethyl imidate hydrochlorides.<sup>16</sup> Holmberg<sup>17</sup> prepared 2-methyl-5-phenyl-1,3,4-thiadiazole by acetylating **11** with carboxymethylthiolacetate, followed by spontaneous cyclization, and by oxidation of acetaldehyde thiobenzhydrazone with ferric chloride.<sup>10</sup> A considerable number of 2-alkyl-5-aryl-1,3,4-thiadiazoles have been prepared by the method of Stollé.<sup>18</sup>

A methyl group attached to a 1,3,4-thiadiazole ring has a reactivity similar to that in the picolines, and benzaldehyde condenses with 2-methyl-5-phenyl-1,3,4-thiadiazole in the presence of zinc chloride to give the 2-styryl derivative.<sup>18</sup> A similar reactivity is shown by 2-acylamino-5-methyl-1,3,4-thiadiazoles,<sup>19, 20</sup> and it is enhanced in quaternary compounds.<sup>21</sup>



Several publications and patents describe the preparation of 2,5-diaryl-1,3,4-thiadiazoles by treatment of mono- or 1,2-diacylhydrazines with phosphorus pentasulfide or by oxidation of thiobenzhydrazones of aromatic aldehydes with ferric chloride. The 2,5-bis-4-pyridyl derivative was prepared by reaction between thioisonicotinamide and hydrazine.<sup>22</sup> Hydroxydithiobenzoates, useful as thioacylating agents in the method of Jensen,<sup>4</sup> are readily available by a new synthetic

<sup>16</sup> H. Weidiger and J. Kranz, *Chem. Ber.* **96**, 1059 (1963).

<sup>17</sup> B. Holmberg, *Arkiv. Kemi, Mineral. Geol.* **25A**, No. 18 (1947).

<sup>18</sup> M. Ohta, *J. Pharm. Soc. Japan* **73**, 1127 (1953); *Chem. Abstr.* **48**, 1291 (1954).

<sup>19</sup> Belgian Patent 597,616 (1961); *Chem. Abstr.* **60**, 15879 (1964).

<sup>20</sup> Belgian Patent 630,163 (1963); *Chem. Abstr.* **60**, 14516 (1964).

<sup>21</sup> British Patent 785, 939 (1957); *Chem. Abstr.* **52**, 10777 (1958).

<sup>22</sup> F. H. McMillan, F. Leonard, R. J. Meltzer, and J. A. King, *J. Am. Pharm. Assoc.* **75**, 457 (1953).



method.<sup>23</sup> Huisgen *et al.*<sup>24</sup> prepared 2-alkyl- and 2-aryl-5-phenyl-1,3,4-thiadiazoles by reaction between 5-alkyl- and 5-aryltetrazoles and thiobenzoyl chloride. Benzonitriliumthiobenzamide (12) is assumed as an intermediate.

### B. POLYHYDROXYALKYL DERIVATIVES

Holmberg<sup>25</sup> has described a large number of products of condensation between 11 and monosaccharides, which are formulated as thiobenzoylhydrazinomonosaccharides (13). These are slightly soluble, well-crystallizing, and generally suitable as derivatives for the characterization of sugars. On oxidation with ferric chloride, potassium persulfate, or *N*-chlorobenzenesulfonamide, the aldose derivatives form the corresponding 2-phenyl-5-polyhydroxyalkyl-1,3,4-thiadiazoles (14), which have characteristically different melting points and optical rotations. Ketose derivatives also form thiadiazoles with fragmentation of the hydroxylated side chain. Thus the product from fructose and 11 on oxidation gives a mixture of 2-hydroxymethyl-5-phenyl-1,3,4-thiadiazole and the 2-phenyl-5-tetrahydroxybutyl-1,3,4-thiadiazole corresponding to D-arabinose.

These compounds are very stable, but as derivatives of aldonic acids they undergo epimerization with hot sodium hydroxide. They are oxidized by hypobromite to salts of the labile 2-phenyl-1,3,4-thiadiazole-5-carboxylic acid (15). The corresponding products from fucose<sup>26</sup> and hexuronic acids<sup>27</sup> were described in later papers.

## III. 1,3,4-Thiadiazoles with Functional Groups

### A. HALOGEN DERIVATIVES

Due to the electronegativity of the two nitrogen atoms in the ring, the carbon atoms have a low electron density, and, consequently, halogeno-1,3,4-thiadiazoles are important intermediates, in which the halogen atom is readily displaced by nucleophiles. The general way of preparing chloro- and bromo-1,3,4-thiadiazoles is by Sandmeyer

<sup>23</sup> R. Gompper, R. R. Schmidt, and E. Kutter, *Ann. Chem.* **684**, 37 (1965); *Chem. Ber.* **98**, 1374 (1965).

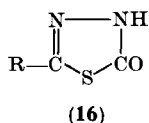
<sup>24</sup> R. Huisgen, H. J. Sturm, and M. Seidel, *Chem. Ber.* **94**, 1555 (1961).

<sup>25</sup> B. Holmberg, *Arkiv Kemi* **4**, 33 (1951).

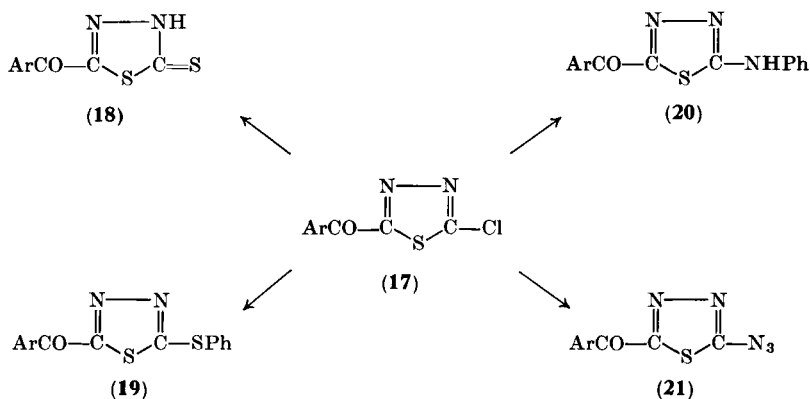
<sup>26</sup> B. Holmberg, *Arkiv Kemi* **7**, 529 (1954).

<sup>27</sup> B. Holmberg, *Arkiv Kemi* **7**, 513 (1954).

reaction of the corresponding amines,<sup>3, 28</sup> used already by Stollé and Fehrenbach.<sup>29</sup> Another standard procedure is reaction of 1,3,4-thiadiazolin-2(3)-ones (16) with phosphorus halides.<sup>30</sup> A patent<sup>31</sup> describes the transformation of potential mercapto compounds to chloro derivatives by refluxing with carbonyl chloride in dioxane. In this way the 2,5-dichloro derivative is also obtained. Potential mercaptothiadiazoles can also be transformed to chloro derivatives via sulfonyl chlorides, which lose sulfur dioxide on pyrolysis.<sup>32</sup>



Bacchetti *et al.*<sup>33, 34</sup> have studied the reaction between aromatic diazoketones and thiocarbonyl chloride. In this reaction the diazo-methyl part is added to the thiocarbonyl group carbon to sulfur and



<sup>28</sup> M. Kanaoka, *J. Pharm. Soc. Japan* **75**, 1149 (1955); *Chem. Abstr.* **50**, 5647 (1956).

<sup>29</sup> R. Stollé and K. Fehrenbach, *J. Prakt. Chem.* [2] **122**, 289 (1929).

<sup>30</sup> E. Testa, G. G. Gallo, F. Fava, and G. Weber, *Gazz. Chim. Ital.* **88**, 812 (1958).

<sup>31</sup> British Patent 913,910 (1962); *Chem. Abstr.* **59**, 2836 (1963).

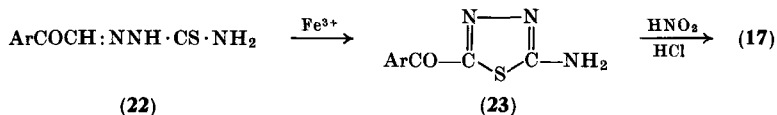
<sup>32</sup> V. Petrow, O. Stephenson, A. J. Thomas, and A. M. Wild, *J. Chem. Soc.*, 1508 (1958).

<sup>33</sup> T. Bacchetti, A. Alemagna, and B. Danieli, *Tetrahedron Letters*, 47 (1964).

<sup>34</sup> T. Bacchetti, A. Alemagna, and B. Danieli, *Ann. Chim. (Rome)* **55**, 615 (1965).

nitrogen to carbon, and 2-acyl-5-chloro-1,3,4-thiadiazoles (**17**) are formed. In thione esters<sup>35</sup> and isothiocyanates<sup>36</sup> the direction of addition is the reverse, and 1,2,3-thiadiazoles are formed.

The chlorothiadiazoles (**17**) react readily with nucleophiles to give a series of 5-substituted 2-acyl-1,3,4-thiadiazoles (**18–21**).<sup>34</sup> The structure of **17** was demonstrated by an unambiguous synthesis from *p*-nitrophenylglyoxal thiosemicarbazone (**22**).<sup>34</sup>



2-Bromo-1,3,4-thiadiazoles can be transformed to the corresponding 2-fluoro compounds by treatment with silver fluoride,<sup>37</sup> but the yield is low and the reaction attended with considerable decomposition.

## B. NITRO DERIVATIVES

2-Nitro-1,3,4-thiadiazole seems to be the only known representative of this class. It was formed in a Sandmeyer reaction between 1,3,4-thiadiazole diazonium chloride and sodium cobaltinitrite in the presence of copper sulfite.<sup>38</sup> An alleged 2-amino-5-nitro-1,3,4-thiadiazole is discussed in Section IV,B.

## C. ALDEHYDE, KETONE, AND CARBOXYLIC ACID DERIVATIVES

The first preparation of 1,3,4-thiadiazole aldehydes was described by Ohta and Isowa,<sup>39</sup> who used the Kröhnke reaction<sup>40</sup> on 2,5-dimethyl- and 2-methyl-5-phenyl-1,3,4-thiadiazole. They described 2,4-dinitrophenylhydrazones and thiosemicarbazones, oxidation to acid, and acyloin condensation. Bacchetti<sup>41</sup> has shown that 2-phenyl-

<sup>35</sup> U. Schmidt, E. Heyman, and K. Kabitzke, *Chem. Ber.* **96**, 1478 (1963).

<sup>36</sup> W. Reid and B. M. Beck, *Ann. Chem.* **673**, 128 (1964).

<sup>37</sup> H. Schroeder, R. Raetz, W. Schnabel, H. Ulrich, E. Kober, and C. Grundmann, *J. Org. Chem.* **27**, 2589 (1962).

<sup>38</sup> U.S. Patent 3,152,017 (1964); *Chem. Abstr.* **62**, 236 (1965).

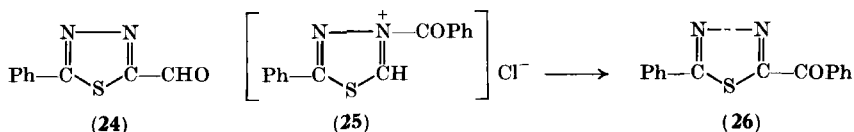
<sup>39</sup> M. Ohta and Y. Isowa, *Nippon Kagaku Zasshi* **79**, 1452 (1958); *Chem. Abstr.* **54**, 5627 (1960).

<sup>40</sup> F. Kröhnke, *Angew. Chem.* **75**, 317 (1963).

<sup>41</sup> T. Bacchetti, personal communication (1966).

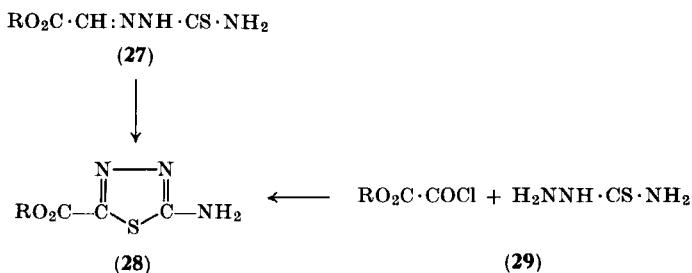
1,3,4-thiadiazole-5-carboxaldehyde (**24**) forms a stable hydrate, which is in accord with the electron-attracting character of the thiadiazole ring.

Ketones of the 1,3,4-thiadiazole series have been described by Holmberg,<sup>10</sup> who oxidized phenylglyoxalthiosemicarbazone (**22**) and obtained 2-amino-5-benzoyl-1,3,4-thiadiazole (**23**), and, as mentioned in Section III,A by Bacchetti.<sup>34</sup> In these compounds, e.g., **19**, the acyl group can be removed by treatment with a catalytic amount of sodium ethoxide in ethanol.



Bacchetti<sup>41</sup> has also prepared 2-benzoyl-5-phenyl-1,3,4-thiadiazole (**26**) by heating 2-phenyl-4-benzoyl-1,3,4-thiadiazolium chloride (**25**) to 200°. **26** also undergoes ethanolysis under basic conditions, but slower than **19**.

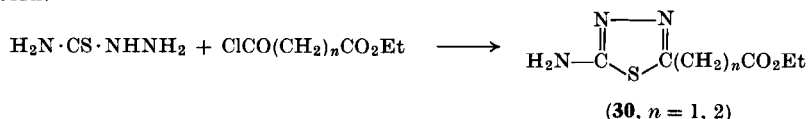
Due to the strong electron attraction of the thiadiazole ring, carboxylic acids with the carboxyl group attached to the ring are rather unstable. Thus Holmberg<sup>25</sup> on acidification of the sodium salt of **15** at room temperature obtained a mixture of 40 % of the acid and 60 % of 2-phenyl-1,3,4-thiadiazole. The acid could be prepared in a pure state by careful oxidation of the corresponding aldehyde (**24**).<sup>39</sup>



Werber and Maggio<sup>42</sup> have shown that electron-donating substituents in position 2 can increase the stability of 1,3,4-thiadiazole carboxylic acids. They oxidized ethyl and butyl glyoxylate thiosemicarbazones (**27**) with ferric chloride and obtained ethyl (butyl)

<sup>42</sup> G. Werber and F. Maggio, *Ann. Chim. (Rome)* **49**, 2124 (1959).

2-amino-1,3,4-thiadiazole-5-carboxylates (**28**). The ethyl ester was also obtained in low yield by condensation of thiosemicarbazide with ethoxalyl chloride (**29**). The oxidative cyclization was also performed with 4-substituted thiosemicarbazones.<sup>43</sup> Acid hydrolysis of **28** caused decarboxylation, but the acid could be obtained by alkaline hydrolysis. It was shown by differential thermal analysis to undergo decarboxylation at 160° in the solid state, though the observed melting point was 191° (2-amino-1,3,4-thiadiazole).<sup>44</sup> At low temperatures even glyoxylic acid thiosemicarbazones could be oxidized with ferric chloride without decarboxylation. One exception was found in the 4-phenylthiosemicarbazone, which reflects the importance of the electron-donating capacity of the amino group to the stability of the acid.



Derivatives of 1,3,4-thiadiazolylacetic and -propionic acids are also known,<sup>45</sup> but they seem to have normal stability. They have been prepared by reaction between thiosemicarbazide and dicarboxylic acid ester chlorides (**30**).

## D. AMINO AND HYDRAZINO DERIVATIVES

### 1. Monoamines and Monohydrazines

There are two main routes to 2-amino-1,3,4-thiadiazoles. One starts from a thiosemicarbazide, and the second carbon atom is introduced with a suitable cyclizing agent. The other route employs a 1,3,4-thiadiazole ring with a substituent, such as a halogen atom or an alkylsulfonyl group, which can be displaced by ammonia or an amine. Less common but sometimes quite useful are methods by which the amino group is introduced with the cyclizing agent without intermediate formation of a semicarbazide or thiosemicarbazide derivative.

For cyclization of thiosemicarbazides a large variety of reagents is available, and several of them have been used from the beginning of the century. This applies, for example, to the reaction with aldehydes to form thiosemicarbazones, which are then cyclized by oxida-

<sup>43</sup> G. Werber and F. Maggio, *Ann. Chim. (Rome)* **51**, 944 (1961).

<sup>44</sup> G. Werber and F. Maggio, *Ann. Chim. (Rome)* **53**, 3 (1963).

<sup>45</sup> M. Ohta, *J. Pharm. Soc. Japan* **72**, 1536 (1952); *Chem. Abstr.* **47**, 9323 (1953).

tion with ferric chloride. This reaction has been widely used also in recent years. A complication was observed in the oxidation of pyridine-2-aldehyde thiosemicarbazone, which went normally only when the sulfur atom was protected by acetylation. Oxidation of the *N,S*-diacetyl derivative with peracetic acid gave a 70% yield of 2-acetyl-amino-5-(2-pyridyl)-1,3,4-thiadiazole.<sup>46</sup>

Another time-honored reaction is the acylation-dehydration of thiosemicarbazides. The acylation is generally performed with an acid chloride, and elimination of water from the intermediate 1-acylthiosemicarbazide is conveniently effected with cold concentrated sulfuric acid<sup>47, 48</sup> or with 100% phosphoric acid.<sup>49, 50</sup> Phosphorus halides have also been used for the last step,<sup>46</sup> and they are stated to give improved yields when added with the acyl halide in a one-step procedure.<sup>51</sup> Cyclization of 1-acylthiosemicarbazides in alkaline medium leads to 1,2,4-triazole derivatives.

The reaction between 1-carbamoylthiosemicarbazide (31) and acetic anhydride merits a special interest, since it has been claimed by Janniah and Guha<sup>52</sup> to give an aminoendoxy-1,3,4-thiadiazole (32). This type of structure has long been refuted for steric reasons, and now Ban<sup>53</sup> and Petrow *et al.*<sup>32</sup> have shown that the primary product in the above reaction is 2-acetylamino-5-methyl-1,3,4-thiadiazole. This was hydrolyzed by acids to Guha's compound, which is in fact 2-amino-5-methyl-1,3,4-thiadiazole (4, R = CH<sub>3</sub>).

Ortho esters have been frequently used as cyclization agents.<sup>54-56</sup> Generally, heating the reagents together is sufficient to effect cyclization, but Kanaoka<sup>28</sup> isolated the intermediate 1-ethoxymethylene-thiosemicarbazide (33) from the reaction between thiosemicarbazide

<sup>46</sup> B. Hemmerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta* **41**, 2058 (1958).

<sup>47</sup> M. Ohta and T. Higashijima, *J. Pharm. Soc. Japan* **72**, 376 (1952); *Chem. Abstr.* **47**, 3856 (1953).

<sup>48</sup> S. V. Solokov and I. Ya. Postovskii, *J. Gen. Chem. USSR (English Transl.)* **30**, 1764 (1960).

<sup>49</sup> E. Hoggarth, *J. Chem. Soc.*, 1163 (1949).

<sup>50</sup> J. Menin, J.-F. Giudicelli, and H. Najer, *Compt. Rend.* **259**, 3563 (1964).

<sup>51</sup> U.S. Patent 2,497,825 (1950); *Chem. Abstr.* **44**, 5919 (1950).

<sup>52</sup> P. C. Guha, *J. Am. Chem. Soc.* **45**, 1036 (1923); S. L. Janniah and P. C. Guha, *ibid.* **52**, 4860 (1930).

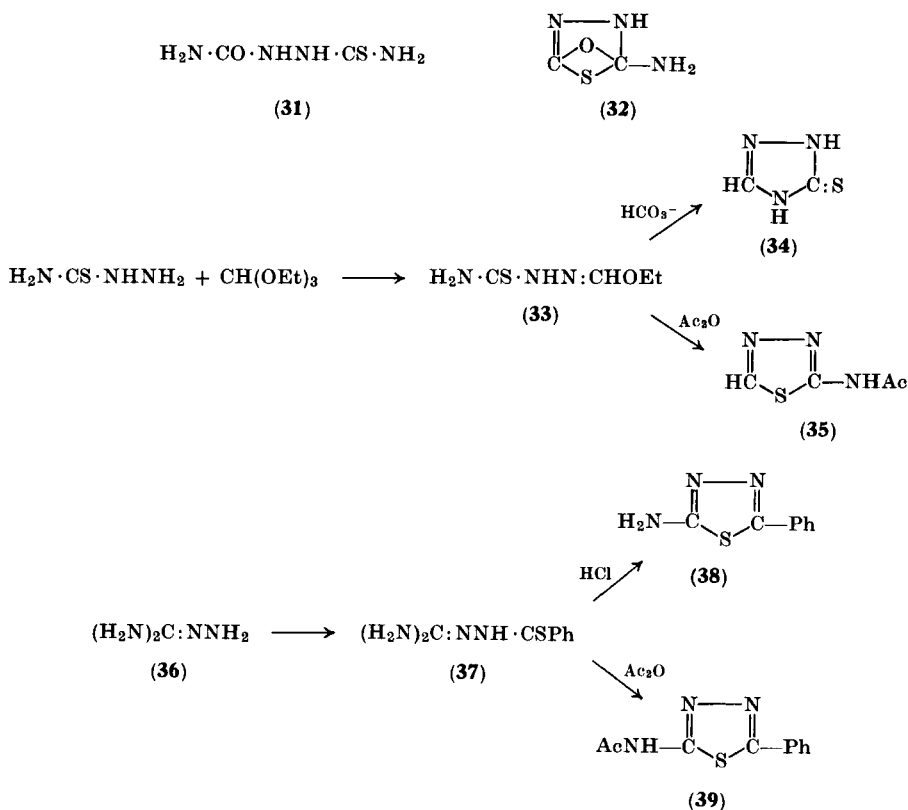
<sup>53</sup> S. Ban, *J. Pharm. Soc. Japan* **74**, 695 (1954); *Chem. Abstr.* **48**, 10741 (1954).

<sup>54</sup> C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.* **77**, 5872 (1955).

<sup>55</sup> C. Ainsworth, *J. Am. Chem. Soc.* **78**, 1973 (1956).

<sup>56</sup> B. Stanovnik and M. Tišler, *J. Org. Chem.* **25**, 2235 (1960).

and triethylorthoformate. Cyclization of **33** with acetic anhydride gave 2-acetylamino-1,3,4-thiadiazole (**35**), whereas on treatment with sodium bicarbonate, 1,2,4-triazoline-3(2)-thione (**34**) was formed. Ainsworth<sup>55</sup> has observed that a mixture of aminothiadiazoles and triazolinethione is formed in the reaction between thiosemicarbazide and triethylorthoacetate.

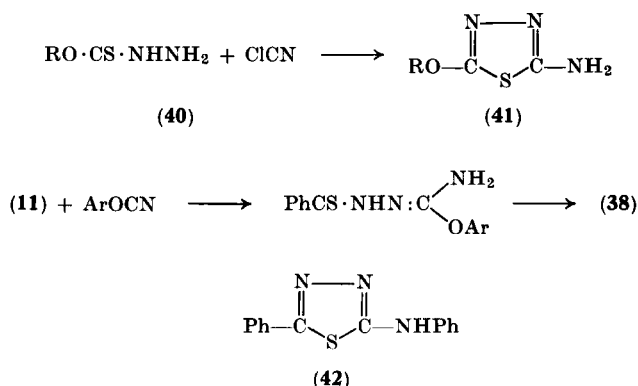


Ethyl imidate hydrochlorides can also be used to cyclize thiosemicarbazides.<sup>16</sup> In acid medium the reaction leads to 2-amino-1,3,4-thiadiazoles, and in basic to 1,2,4-triazoline-3(2)-thiones. Possibly the ethoxymethylene derivatives corresponding to **33** are intermediates in this case also.

Aminoguanidine (**36**) can be used instead of thiosemicarbazide, but then cyclization must be performed with a thioacylating agent. Thus

thiobenzoylation of **36** with carboxymethyl dithiobenzoate gives *N*-thiobenzamidoguanidine (**37**), which is cyclized by hot hydrochloric acid to 2-amino-5-phenyl-1,3,4-thiadiazole (**38**) and by acetic anhydride to the corresponding 2-acetylmino derivative (**39**).<sup>57</sup>

In some cases a reagent can be used for cyclizing thiohydrazides, which itself provides an amino group. Thus thioncarbazates (**40**) are cyclized by cyanogen chloride and cyanogen bromide to 2-alkoxy-5-amino-1,3,4-thiadiazoles (**41**).<sup>58</sup>



Aryl cyanates serve the same purpose in reactions with **11**, which lead to **38**.<sup>59</sup>

When 5-phenyltetrazole reacted with phenylisothiocyanate, 2-anilino-5-phenyl-1,3,4-thiadiazole (**42**) was formed.<sup>12</sup>

Nucleophilic substitution in the thiadiazole ring could be of value as a way of preparing aminothiadiazoles corresponding to thiosemicarbazides which are not readily available. This case does not frequently occur, but the method has been of considerable use in the preparation of hydrazinothiadiazoles. Thus, Fujii *et al.*<sup>60</sup> prepared 2-hydrazino-5-phenyl-1,3,4-thiadiazole (**43**) by hydrazinolysis of 2-methylsulfonyl-5-phenyl-1,3,4-thiadiazole (**44**), and Kanaoka<sup>28</sup> prepared the 5-methyl analog by hydrazinolysis of 2-chloro-5-methyl-1,3,4-thiadiazole. Both authors also obtained these compounds by

<sup>57</sup> F. Kurzer, *J. Chem. Soc.*, 1617 (1961).

<sup>58</sup> British Patent, 916,061 (1963); *Chem. Abstr.* **59**, 1650 (1963).

<sup>59</sup> E. Grigat and R. Puetter, *Chem. Ber.* **98**, 1359 (1965).

<sup>60</sup> K. Fujii, H. Yoshikawa, and M. Yuasa, *J. Pharm. Soc. Japan* **74**, 1056 (1954); *Chem. Abstr.* **49**, 11592 (1955).



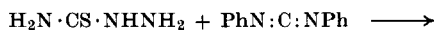
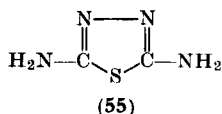


(48) with hot concentrated hydrochloric acid gave 2-hydrazino-1,3,4-thiadiazolin-5(4)-thione (49). 1,5-Bisthiocarbamoylthiocarbohydrazide (50) under the same treatment formed 2-amino-5-hydrazino-1,3,4-thiadiazole (51).<sup>63</sup>

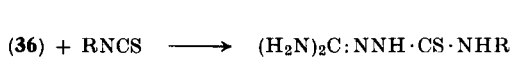
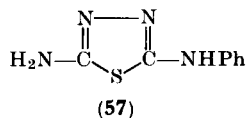
Oxidation of bisaldothiocarbohydrazones (52) with ferric chloride,<sup>64</sup> or cyclization of monothiocarbohydrazones (53) with thioacylating agents, leads to thiadiazolylhydrazones (54), from which hydrazino-thiadiazoles can be prepared in some cases.<sup>65</sup>

## 2. Diamines

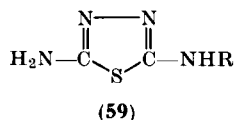
2,5-Diamino-1,3,4-thiadiazole (55) was formed in 25 % yield by the action of phosphorus oxychloride on 1-carbamoylthiosemicarbazide (31).<sup>66</sup>



(56)



(58)



By cyclizing thiosemicarbazide with *N,N'*-diphenylcarbodiimide, Goodfrey and Kurzer<sup>67</sup> obtained 2-amino-5-anilino-1,3,4-thiadiazole (57) with the thiocarbamidoaminoguanidine (56) as intermediate. 57 and similar compounds (59), also with alkylamino groups, have

<sup>63</sup> H. Beyer and C.-F. Kröger, *Ann. Chem.* **637**, 126 (1960).

<sup>64</sup> J. Sandström, *Arkiv Kemi* **9**, 255 (1956).

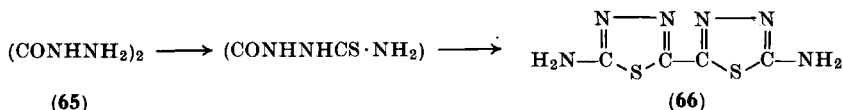
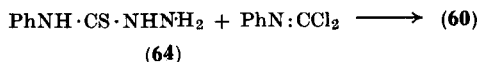
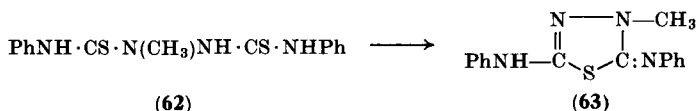
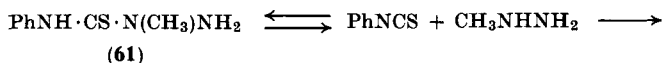
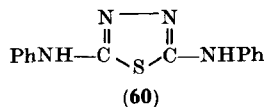
<sup>65</sup> J. Sandström, *Acta Chem. Scand.* **14**, 1037 and 1939 (1960); **15**, 1295 (1961); **17**, 1595 (1963).

<sup>66</sup> H. Gehlen and K. Moeckel, *Ann. Chem.* **685**, 176 (1965).

<sup>67</sup> L. E. A. Goodfrey and F. Kurzer, *J. Chem. Soc.*, 3561 (1962).

been prepared from aminoguanidine and isothiocyanates via 1-aminothiosemicarbazides (58).<sup>68, 69</sup> Thiadiazoles were obtained by cyclization in acid medium, whereas bases gave triazoles. The intermediates (58) were conveniently isolated as the sparingly soluble tosylates.

2,5-Dianilino-1,3,4-thiadiazole (60) has been prepared in reasonable yield by heating of 4-phenylthiosemicarbazide in a high-boiling inert solvent.<sup>70, 71</sup> Since 2-methyl-4-phenylthiosemicarbazide (61) forms 2-phenylimino-3-methyl-5-anilino- $\Delta^4$ -1,3,4-thiadiazoline (63) under the same conditions, the authors conclude that the reaction proceeds



with splitting of the thiosemicarbazide to hydrazine and isothiocyanate, followed by formation of a bithiourea (62) and cyclization of this. However, a direct attack of one molecule of 61 on another with elimination of methylhydrazine should also give 62 and 63.

60 was also obtained in good yield by cyclization of 4-phenylthiosemicarbazide with *N*-dichloromethyleneaniline (64).<sup>72</sup>

<sup>68</sup> L. E. A. Goodfrey and F. Kurzer, *J. Chem. Soc.*, 5137 (1962).

<sup>69</sup> F. Kurzer and J. Canelle, *Tetrahedron* **19**, 1603 (1963).

<sup>70</sup> B. Stanovnik and M. Tisler, *J. Org. Chem.* **26**, 5200 (1961).

<sup>71</sup> B. Stanovnik and M. Tišler, *Croat. Chem. Acta* **36**, 169 (1964).

<sup>72</sup> K. Moeckel and H. Gehlen, *Z. Chem.* **4**, 388 (1964).

An interesting diamine, bi-[5-(2-amino-1,3,4-thiadiazolyl)] (**66**), was prepared by Kabo and Ohta<sup>73</sup> from oxalic acid dihydrazide (**65**).

### 3. Reactions of Amino-1,3,4-thiadiazoles

Though the aminothiadiazoles are rather weak bases, they are nucleophilic enough to be readily acetylated by acid chlorides. Aromatic sulfonyl chlorides have been very frequently used, since the resulting sulfonamides are of considerable pharmaceutical interest. Deacylation is generally performed in hot acid solution without destroying the ring.

2-Acylamino-1,3,4-thiadiazoles have been reduced with lithium aluminium hydride to the corresponding 2-alkylamino derivatives.<sup>74</sup>

2-Amino-5-aryl-1,3,4-thiadiazoles have been found to undergo the Mannich reaction with a variety of methylene compounds.<sup>75</sup>

Schiff bases (**67**) are formed by reaction between 2-amino-1,3,4-thiadiazoles and aromatic aldehydes.<sup>76</sup> When  $R = NH_2$ , only a monocondensation product is formed.

In most cases, 2-amino-1,3,4-thiadiazoles are alkylated on the ring nitrogen atom in position 3 (**68**).<sup>30, 77</sup> 2-Acylamino-<sup>78</sup> and 2-tosylamino-1,3,4-thiadiazoles (**69**)<sup>79</sup> are alkylated in the same position by alkyl halides in alkaline medium. One case is known, however, where the base directs the alkylating agent. 2-Acetylthio-1,3,4-thiadiazole (**70**) was methylated in the ring to **71** by methyl bromide and sodium methoxide (*a*), but in the acetylthio group to **72** by methyl iodide and potassium *tert*-butoxide in *tert*-butyl alcohol (*b*).<sup>80</sup>

Bacchetti<sup>81</sup> has found new ways to ring-alkylated iminothiadiazolines (**74**), starting from  $\alpha$ -chlorobenzaldehyde hydrazones (**73**).

<sup>73</sup> H. Kabo and M. Ohta, *Nippon Kagaku Zasshi* **78**, 1588 (1957); *Chem. Abstr.* **54**, 1502 (1960).

<sup>74</sup> E. Testa, G. G. Gallo, and F. Fava, *Gazz. Chim. Ital.* **88**, 1272 (1958).

<sup>75</sup> R. M. Senapati, K. K. Patnaik, and M. K. Rout, *J. Proc. Inst. Chemists (India)* **37**, 111 (1965).

<sup>76</sup> M. Ohta, H. Oya, and A. Mifune, *J. Pharm. Soc. Japan* **73**, 852 (1953); *Chem. Abstr.* **48**, 10006 (1954).

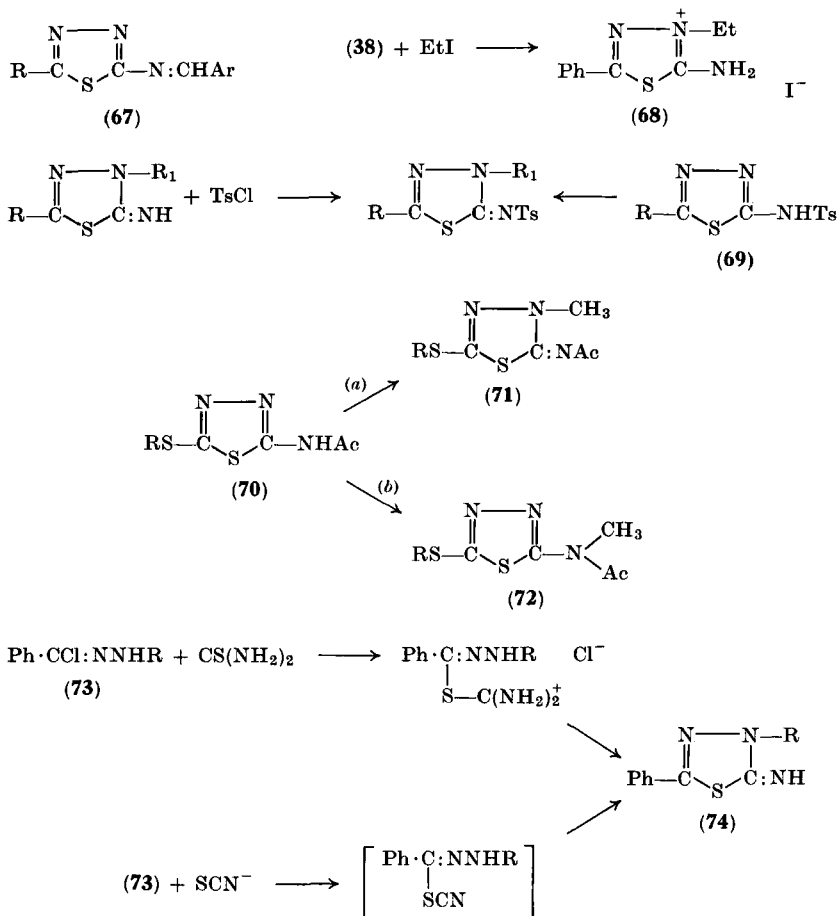
<sup>77</sup> J. Goerdeler and W. Roth, *Chem. Ber.* **96**, 534 (1963).

<sup>78</sup> G. Pala, *Farmaco (Pavia)*, (*Ed. Sci.*) **13**, 650 (1958).

<sup>79</sup> M. Kanaoka, *Yakugaku Zasshi* **81**, 1378 (1961); *Chem. Abstr.* **56**, 7305 (1962).

<sup>80</sup> R. W. Young, K. H. Wood, J. A. Eichler, J. R. Vaughan, Jr., and G. W. Anderson, *J. Am. Chem. Soc.* **78**, 4649 (1956).

<sup>81</sup> T. Bacchetti, *Gazz. Chim. Ital.* **91**, 866 (1961).

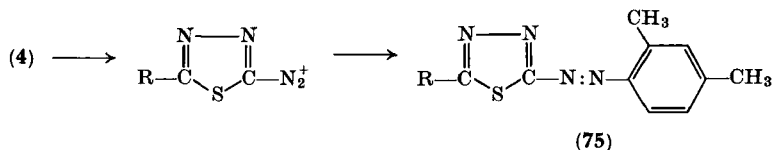


### E. DIAZO, AZO, AND AZIDO DERIVATIVES

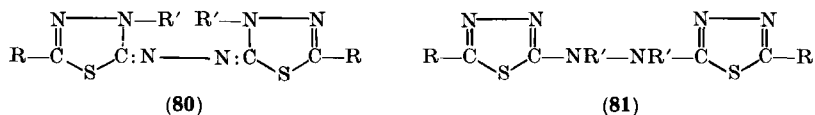
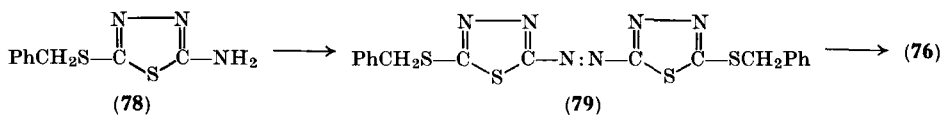
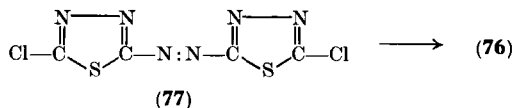
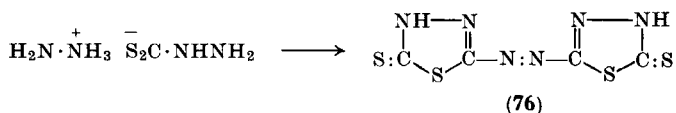
Stollé and Fehrenbach<sup>29</sup> investigated extensively the diazotization of 2-amino-1,3,4-thiadiazoles, which was found to go smoothly in sufficiently strongly acid solution. Goerdeler *et al.*<sup>82</sup> later pointed out the remarkably strong coupling activity of diazonium salts derived from 1,2,4- and 1,3,4-thiadiazoles. They even observed coupling with *m*-xylene to **75** and with mesitylene in high yield.

<sup>82</sup> J. Goerdeler, H. Haubrich, and J. Galinke, *Chem. Ber.* **93**, 397 (1960).

Azothiadiazoles have been prepared by oxidation of aminothiadiazoles with calcium hypochlorite.<sup>29</sup> More recently, Petri and Glemser<sup>83, 84</sup> obtained a new azothiadiazole, 2,2'-azo-1,3,4-thiadiazoline-5(4)-thione (**76**), by oxidation of hydrazinium dithiocarbazate



with thionyl chloride. The yield was not more than 0.2%, and the dark red compound was isolated by chromatography on cellulose powder. It could also be obtained in good yield by reaction between 5,5'-dichloro-2,2'-azo-1,3,4-thiadiazole (**77**)<sup>29</sup> and sodium sulfide.

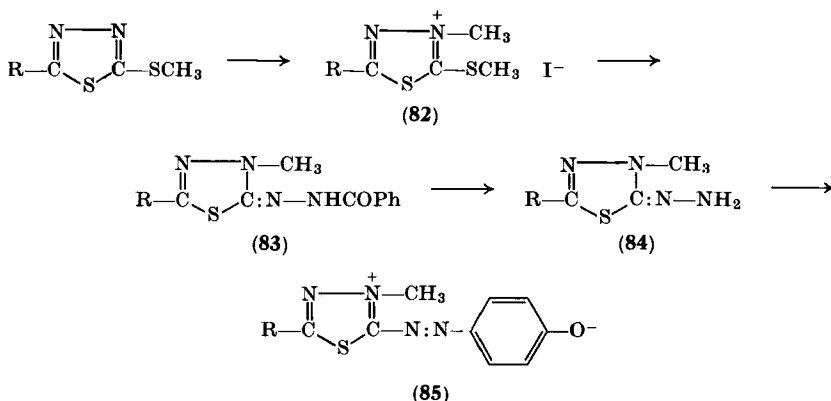


The *S*-benzyl derivative (**79**) could be obtained by oxidation of 2-amino-5-benzylthio-1,3,4-thiadiazole (**78**) with calcium hypochlorite or potassium permanganate. **79** could be debenzylated to **76** by sodium in liquid ammonia. **76** was smoothly reduced by hydrogen sulfide to a dihydro derivative, which was rapidly reoxidized by air. **76** could be transformed into *S*-alkyl derivatives, e.g. **79**, which were

<sup>83</sup> N. Petri and O. Glemser, *Chem. Ber.* **94**, 553 (1961).

<sup>84</sup> N. Petri and O. Glemser, *Chem. Ber.* **94**, 566 (1961).

similarly reduced. These dihydro derivatives were more resistant to oxidation. They were formulated as thiadiazolinone azines (**80**,  $R' = H$ ) rather than as hydrazothiadiazoles (**81**,  $R' = H$ ). Methylation of the dihydro derivative (**80**, **81**) with dimethyl sulfate in alkaline medium gave 4,4'-dimethyl derivatives (**80**,  $R' = CH_3$ ), and with acetic anhydride the corresponding diacetyl derivatives (**80**,  $R' = Ac$ ) were obtained. By reductive acetylation of **79** with zinc and acetic anhydride, an isomeric diacetyl derivative (**81**,  $R = Ac$ ) was prepared.<sup>83</sup>



Hünig and Oette<sup>85</sup> prepared azothiadiazoles (**85**) by oxidative coupling of 3-methyl-1,3,4-thiadiazolin-2(3)-one hydrazones (**84**) with phenols and diphenylamine. **84** was prepared by reaction of 2-methylthio-3-methyl-1,3,4-thiadiazolium ions (**82**) with benzhydrazide and hydrolysis of the first formed benzhydrazone (**83**). The coupling to **85** was performed with potassium ferricyanide in alkaline medium.

Azido-1,3,4-thiadiazoles (**87**) can be prepared by reaction of hydrazinothiadiazoles (**86**) with nitrous acid,<sup>86</sup> and by reaction of halogenothiadiazoles with sodium azide.<sup>34</sup> Like similar heterocyclic azides<sup>87, 88</sup> they may exist as true azides (**87**) or as tetrazolothiadiazoles (**88**). Kanaoka<sup>86</sup> prefers the bicyclic formulation when  $R = Ph$ , but Bacchetti *et al.*<sup>34</sup> have shown that in the solid state the compound

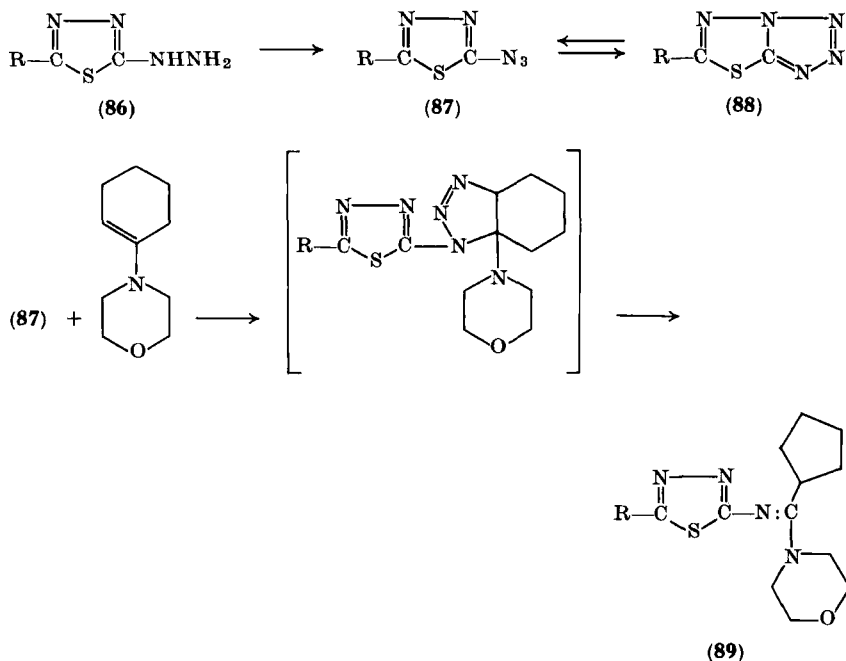
<sup>85</sup> S. Hünig and K.-H. Oette, *Ann. Chem.* **641**, 94 (1961).

<sup>86</sup> M. Kanaoka, *Chem. & Pharm. Bull. (Tokyo)* **6**, 382 (1958); *Chem. Abstr.* **53**, 3200 (1959).

<sup>87</sup> J. H. Boyer and E. J. Miller, Jr., *J. Am. Chem. Soc.* **81**, 4671 (1959).

<sup>88</sup> C. Temple, Jr. and J. A. Montgomery, *J. Am. Chem. Soc.* **86**, 2946 (1964).

with  $R = p$ -chlorobenzoyl shows an infrared absorption band at  $2160\text{ cm}^{-1}$ , characteristic of an azido group. Since azido derivatives of pyridine, pyrimidine, 1,2,4-triazine, and benzthiazole, capable of the isomerism mentioned above, show no azido band in the solid state but do so in solution,<sup>87, 88</sup> the authors<sup>34</sup> conclude that the equilibrium  $(87) \rightleftharpoons (88)$  must be well on the azide side. As further evidence a reaction with morpholino cyclohexene is described, which proceeds



with addition of the azido group to the enamine double bond, followed by elimination of nitrogen and ring contraction to give the amidine (89). However, though this is an interesting reaction, it gives no indication regarding the position of the equilibrium  $(87) \rightleftharpoons (88)$ .

In two other cases ( $87$ ,  $R = Ph$  and  $CH_3S$ ), azido bands in the infrared have been observed at  $2120\text{ cm}^{-1}$  in the solid state,<sup>89</sup> so it is probable that the azido form ( $87$ ) in general is the more stable in these systems.

<sup>89</sup> J. Sandström, unpublished results.

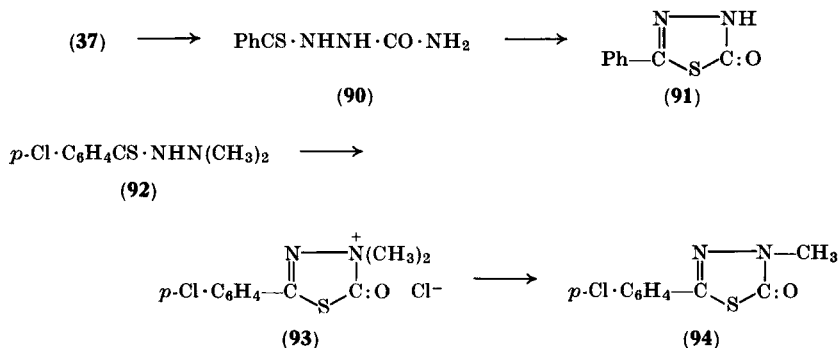


## F. POTENTIAL HYDROXY DERIVATIVES

## 1. Free "Hydroxy-1,3,4-thiadiazoles"

"Hydroxy-1,3,4-thiadiazoles" have in several cases been shown to exist mainly as 1,3,4-thiadiazolinones, at least in the solid state. For the preparation of compounds of this class, several routes are available:

- (a) cyclization of *N*-carbamoylthiohydrazides and analogous compounds;
- (b) cyclization of suitable thiohydrazides with carbonyl chloride;
- (c) hydrolysis of 1,3,4-thiadiazoles with labile substituents;
- (d) oxidation of the corresponding 1,3,4-thiadiazolinethiones.



Method (a) has been used by Kurzer,<sup>57</sup> who hydrolyzed *N*-thiobenzamidoguanidine (37) to 1-carbamoyl-2-thiobenzoylhydrazine (90). This was cyclized by heat to 2-phenyl-1,3,4-thiadiazolin-5(4)-one (91).

Method (b) has old traditions, but no recent applications seem to have been reported. In method (c), methylsulfonyl<sup>60</sup> and carboxymethylsulfonyl-1,3,4-thiadiazoles<sup>90-92</sup> have been used as starting materials. Even the carboxymethylthio group is sufficiently labile to undergo displacement by the hydroxide ion.<sup>93</sup>

<sup>90</sup> T. Sato and M. Ohta, *J. Pharm. Soc. Japan* **75**, 1535 (1955); *Chem. Abstr.* **50**, 10728 (1956).

<sup>91</sup> G. Maffi, E. Testa, and R. Ettorre, *Farmaco (Pavia)*, (*Ed. Sci.*) **13**, 187 (1958).

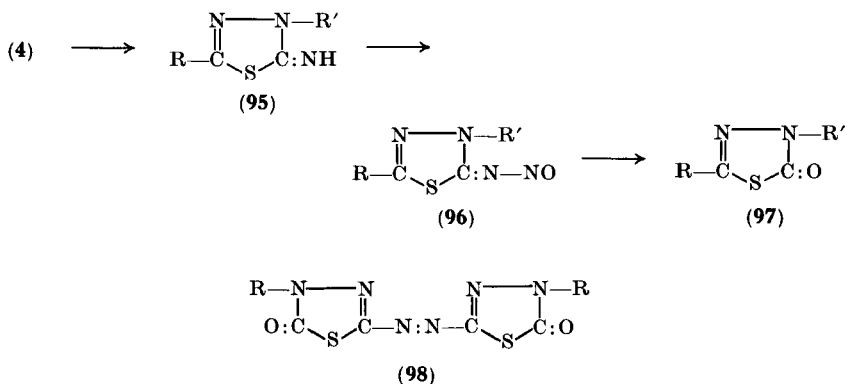
<sup>92</sup> H. Ohta and M. Ohta, *Nippon Kagaku Zasshi* **78**, 700 (1957); *Chem. Abstr.* **53**, 6217 (1959).

<sup>93</sup> H. Ueda and M. Ohta, *Nippon Kagaku Zasshi* **80**, 571 (1959); *Chem. Abstr.* **55**, 4509 (1961).

Method (*d*) has been used by Petri and Glemser,<sup>83</sup> who oxidized the azo-1,3,4-thiadiazolinethione (76) with hydrogen peroxide to the corresponding azo-1,3,4-thiadiazolinone in good yield.

## 2. *N*-Substituted 1,3,4-Thiadiazolinones

These compounds can in principle, with suitable modifications, be prepared by all the methods (*a*)–(*d*) in the previous section. In this case (*c*) would have to be applied to 1,3,4-thiadiazolium ions, e.g. **82**. An interesting modification of method (*b*) has been described by Meyer and Cummings.<sup>94</sup> 1,1-Dimethyl-2-*p*-chlorothiobenzoylhydrazine (**92**) reacted with carbonyl chloride to give a product,



presumably **93**, which by moderate heat was decomposed to give 2-*p*-chlorophenyl-1,3,4-thiadiazolin-5(4)-one (**94**) in excellent yield.

Åkerblom and Skagius<sup>95, 96</sup> and Skagius<sup>97</sup> have prepared 3-alkyl-1,3,4-thiadiazolin-2(3)-ones (**95**) from aminothiadiazoles (**4**) by ring-alkylation to **95**, nitrosation of the imino group to **96**, and thermal decomposition of the nitrosamine to **97**. The reaction seems to be quite general, since it has been performed with R = amino,<sup>95</sup> alkoxy,<sup>96</sup> and 2-nitro-5-furyl.<sup>97</sup>

<sup>94</sup> R. F. Meyer and B. L. Cummings, *J. Heterocyclic Chem.* **1**, 186 (1964).

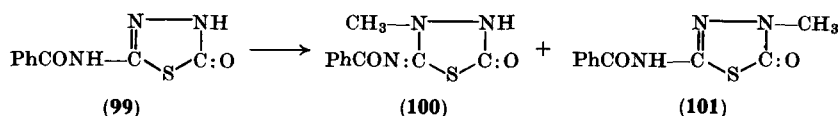
<sup>95</sup> E. Åkerblom and K. Skagius, *Acta Chem. Scand.* **16**, 1103 (1962).

<sup>96</sup> E. Åkerblom and K. Skagius, *Acta Chem. Scand.* **18**, 174 (1964).

<sup>97</sup> K. Skagius, *Nitro Compds., Proc. Intern. Symp., Warsaw, 1963* p. 475. Pergamon Press, Oxford, 1964; *Chem. Abstr.* **63**, 18086 (1965).

Direct alkylation of 1,3,4-thiadiazolinones seems to give the *N*-alkyl derivatives (97). Thus, 2,2'-azo-1,3,4-thiadiazolin-5(4)-one was benzylated with benzyl chloride in alkaline medium to give 2,2'-azo-4,4'-dibenzyl-1,3,4-thiadiazolin-5(4)-one (98).<sup>83</sup> The presence of carbonyl groups in 98 is demonstrated by a strong carbonyl absorption band in the infrared spectrum.

2-Benzamido-1,3,4-thiadiazolin-5(4)-one (99) was methylated by dimethyl sulfate and alkali to a mixture of the 3-methyl (100) and the 4-methyl (101) derivatives.<sup>95</sup> The structures of 100 and 101 were demonstrated by analysis and infrared spectra.



### 3. Alkoxy-1,3,4-thiadiazoles

*O*-Alkylation of 1,3,4-thiadiazolinones has been claimed,<sup>92</sup> but no proof was given, and, with regard to the results discussed in the previous section, the claims may be regarded with suspicion. More satisfactory routes to alkoxy-1,3,4-thiadiazoles are found in cyclization of alkylthioncarbazates. Thus ethyl thioncarbazate (40, R = Et) reacted with carboxymethyl dithiobenzoate to give 2-ethoxy-5-phenyl-1,3,4-thiadiazole (102), probably with ethyl 3-thiobenzoylthioncarbazate (103) as unisolated intermediate.<sup>98</sup> 102 was also obtained by reaction between thiobenzhydrazide (11) and *O*-ethyl-*S*-carboxymethyl dithiocarbonate.<sup>17</sup>

A patent<sup>99</sup> describes the cyclization of 3-acylthioncarbazates with concentrated sulfuric acid at 0°, and methyl 3-(*N*-benzoylthiocarbamoyl)thioncarbazate (104) is cyclized by heat to 2-benzamido-5-methoxy-1,3,4-thiadiazole (105).<sup>95</sup> The preparation of 2-alkoxy-5-amino-1,3,4-thiadiazoles (41) by cyclization of thioncarbazates with cyanogen halides<sup>58</sup> has been mentioned in an earlier section (III,D,1).

The method of Fromm *et al.*<sup>100</sup> of cyclizing 1,2-bisthioacylhydrazines by oxidation has found use in the preparation of 2-alkoxy-5-amino-1,3,4-thiadiazoles (41). Thus methyl 3-thiocarbamoylthioncarbazate

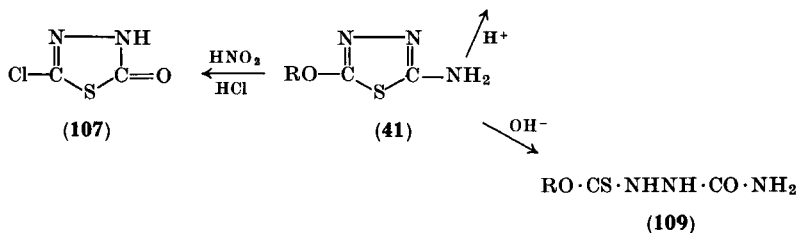
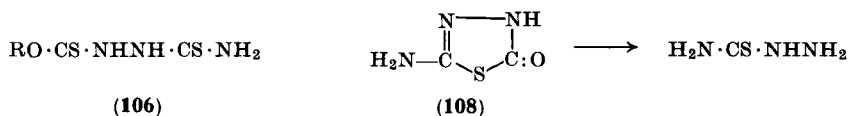
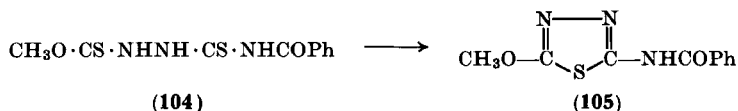
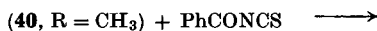
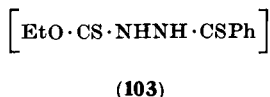
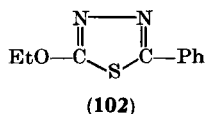
<sup>98</sup> J. Wangel, *Arkiv Kemi* **1**, 431 (1949).

<sup>99</sup> French Patent 1,373,290 (1964); *Chem. Abstr.* **62**, 4033 (1965).

<sup>100</sup> E. Fromm, E. Layer, and K. Nerz, *Ann. Chem.* **433**, 1 (1923).

(106,  $R = \text{CH}_3$ ) on oxidation with hydrogen peroxide gave **41** ( $R = \text{CH}_3$ ). The same reaction has been performed with 4-substituted 1-alkoxythiocarbonylthiosemicarbazides.<sup>96</sup>

In principle, alkoxy-1,3,4-thiadiazoles should be available through reaction of alkoxides with suitable halogenothiadiazoles. However,



cleavage of the thiadiazole ring has been found to occur simultaneously, and in most cases the method is not suitable. 2-Amino-5-chloro-1,3,4-thiadiazole reacted smoothly with phenoxide ion to give **41** ( $R = \text{Ph}$ ), but alkoxide ions caused polymerization. 2-Acetylamino-5-chloro-1,3,4-thiadiazole reacted more sluggishly, but only with sodium methoxide could a low yield of alkoxythiadiazole be obtained; sodium ethoxide gave none of the desired product.<sup>96</sup>

2-Alkoxy-5-amino-1,3,4-thiadiazoles (**41**) are not particularly stable to hydrolysis. They were hydrolyzed by hot hydrochloric acid, first to 2-amino-1,3,4-thiadiazolin-5(4)-one (**108**) (or the tautomeric imine) and then to thiosemicarbazide. On diazotization in hydrochloric acid **41** gave 2-chloro-1,3,4-thiadiazolin-5(4)-one (**107**), and by hot alkali it was cleaved to 1-alkoxythiocarbonylsemicarbazide (**109**).<sup>96</sup>

## G. POTENTIAL MERCAPTO DERIVATIVES

## 1. Free "Mercapto-1,3,4-thiadiazoles"

As will be discussed later (Section V,C), "mercapto-1,3,4-thiadiazoles" have been shown to exist mainly as the tautomeric thiones. They can be prepared in different ways:

- (a) by reaction between thiohydrazides and carbon disulfide, generally in alkaline medium, probably with 3-thioacyldithiocarbazates as unisolated intermediates;
- (b) by dehydrating cyclization of 3-acyldithiocarbazates, which are available from carboxylic acid hydrazides and carbon disulfide in alkaline medium;
- (c) by reaction of 2-halogeno-1,3,4-thiadiazoles with suitable sulfur nucleophiles, such as sodium hydrogen sulfide, thiourea, or sodium thioacetate;
- (d) by sulfuration of 1,3,4-thiadiazolinones and other suitable compounds with phosphorus pentasulfide.

Method (a) has been used by Jensen and Pedersen,<sup>4</sup> who prepared 2-phenyl-1,3,4-thiadiazoline-5(4)-thione (**110**) in 94% yield from thiobenzhydrazide (**11**) and carbon disulfide in ethanolic potassium hydroxide at room temperature. The 2-benzyl analog was obtained in the same way from phenylthioacethydrazide. This method will probably gain importance through the increased availability of thiohydrazides due to the work of Jensen *et al.*<sup>101</sup> Thiosemicarbazide has been used for the preparation of 2-amino-1,3,4-thiadiazoline-5(4)-thione (**111**) in 92% yield through reaction with carbon disulfide in ethanol in an autoclave at 140° without a base,<sup>102</sup> and in 82% yield through reaction with carbon disulfide and sodium carbonate in refluxing ethanol.<sup>32</sup>

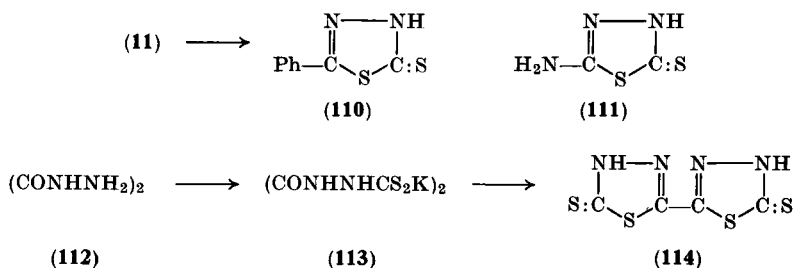
Method (b) has been used in the preparation of 2,2'-bis-1,3,4-thiadiazoline-5(4)-thione (**114**) from oxalic acid dihydrazide (**112**) via the dipotassium bisdithiocarboxylate (**113**).<sup>73</sup> The dehydration-cyclization of **113** was performed with concentrated sulfuric acid.

Method (c) was employed by Goerdeler *et al.*,<sup>3</sup> who obtained 1,3,4-thiadiazoline-2(3)-thione from 2-bromo-1,3,4-thiadiazole (**5**, R=H)

<sup>101</sup> K. A. Jensen, H. R. Baccaro, O. Buchardt, G. E. Olsen, C. Pedersen, and J. Toft, *Acta Chem. Scand.* **15**, 1109 (1961).

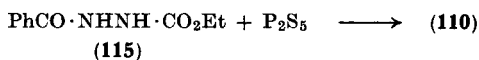
<sup>102</sup> G. Pala, *Ann. Chim. (Rome)* **49**, 1464 (1959).

and thiourea. An intermediate, presumably an isothiuronium salt, was decomposed with alkali to give the desired product in 75% yield.



Bacchetti *et al.*<sup>34</sup> used the same method, and also the reaction with sodium hydrogen sulfide, to prepare 2-aryl-1,3,4-thiadiazoline-5(4)-thiones (18).

Simultaneous sulfuration and cyclization of ethyl 3-benzoyl-carbazate (115) with phosphorus pentasulfide has been found to give 110 in 17% yield.<sup>91</sup> The same compound was prepared by Ainsworth<sup>15</sup> by reaction between 2-phenyl-1,3,4-thiadiazole and phosphorus pentasulfide.



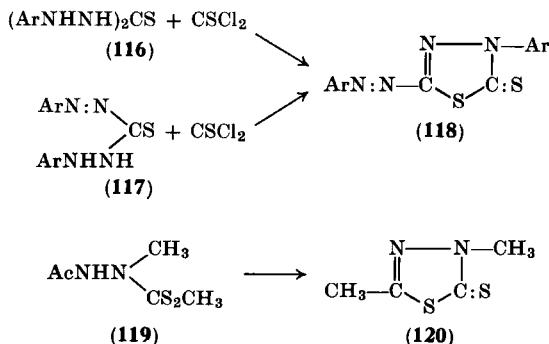
## 2. *N*-Substituted 1,3,4-Thiadiazolinethiones

These compounds can be prepared by the methods (a)–(d) of the previous section with the same modification concerning method (c) as for the corresponding oxygen compounds (Section III, F, 2). Particularly 3-phenyl-1,3,4-thiadiazoline-2(3)-thiones have for a long time been prepared according to method (a) with *N*-phenyl-*N*'-thioacylhydrazines as readily available starting materials. The same result can be achieved with thiocarbonyl chloride as cyclizing agent. Dubenko and Pel'kis<sup>103</sup> have reinvestigated the interaction of this reagent with 1,5-diarylthiocarbohydrazides (116) and diaryldithizones (117) in benzene solution. In both cases the products were 2-arylo-4-aryl-1,3,4-thiadiazoline-5(4)-thiones (118). Since the yields were

<sup>103</sup> R. G. Dubenko and P. S. Pel'kis, *J. Gen. Chem. USSR (English Transl.)* **33**, 282 (1963).

always higher than 50 %, air oxidation had probably occurred in the former case.

The 4-alkyl-1,3,4-thiadiazoline-5(4)-thiones are not generally as easily prepared as the 4-phenyl analogs, due to difficulties involved



in the preparation of 1-alkyl-2-thioacylhydrazines. Direct alkylation of 1,3,4-thiadiazolinethiones with alkyl halides in alkaline medium gives only *S*-alkylation. Diazomethane and 2-phenyl-1,3,4-thiadiazoline-5(4)-thione (110) gave a mixture of *N*- and *S*-methyl derivative, whereas the 2-methyl analog of 110 gave only *S*-methylation.<sup>104</sup> A more general method should be reactions of type (d) of the previous section. The preparation of 2,4-dimethyl-1,3,4-thiadiazoline-5(4)-thione (120) by cyclization of methyl 2-methyl-3-acetyldithiocarbazate (119) with phosphorus oxychloride<sup>104</sup> can probably also be extended to systems with other substituents in positions 2 and 4.

The reaction between 1,1-dimethyl-2-*p*-chlorothiobenzoylhydrazine (92) and thiocarbonyl chloride gave 2-*p*-chlorophenyl-4-methyl-1,3,4-thiadiazoline-5(4)-thione in good yield.<sup>94</sup>

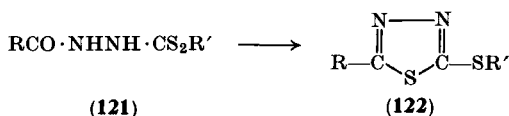
### 3. Alkylthio-1,3,4-thiadiazoles

These can in general be prepared by direct alkylation of 1,3,4-thiadiazolinethiones. Cyclization of alkyl 3-acyldithiocarbazates (121) with sulfuric acid, phosphoric acid, or toluenesulfonic acid, the latter in benzene solution, also leads to 5-substituted 2-alkylthio-1,3,4-thiadiazoles (122).<sup>105</sup> Carboxymethylthio-1,3,4-thiadiazoles can be prepared by reaction between "mercaptothiadiazole" salts and

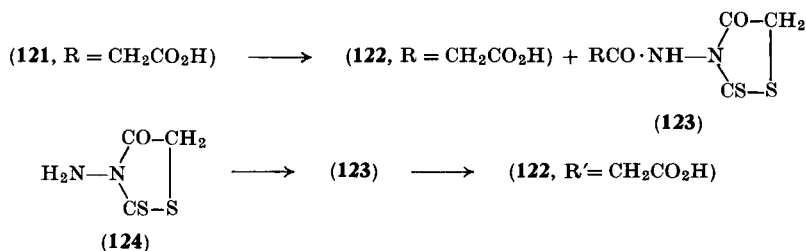
<sup>104</sup> J. Sandström and I. Wennerbeck, *Acta Chem. Scand.* **20**, 57 (1966).

<sup>105</sup> R. W. Young and K. H. Wood, *J. Am. Chem. Soc.* **77**, 400 (1955).

sodium monohalogenoacetates, but also by reaction between potassium 3-acyldithiocarbazates and sodium monohalogenoacetates.



Thus potassium 3-benzoyldithiocarbazate and sodium monochloroacetate after acidification gave a mixture of **122** (R=Ph, R'=CH<sub>2</sub>COOH) and 3-benzoylaminorhodanine (**123**, R=Ph).<sup>90</sup> **123** underwent ring-opening and recyclization to **122** (R=Ph, R'=CH<sub>2</sub>COOH) in hot hydrochloric acid. **123** is also available through acylation of



3-aminorhodanine (**124**).<sup>93</sup> By the latter method 2-carboxymethylthio-1,3,4-thiadiazoles with a considerable variation in R have been obtained.<sup>93</sup>

## H. SULFONYL DERIVATIVES

### 1. Sulfonic Acid Derivatives

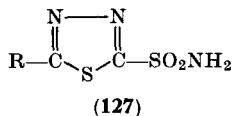
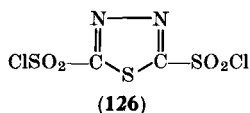
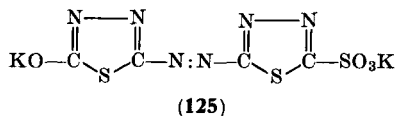
Sulfonic acids of simple 1,3,4-thiadiazoles appear not to have been prepared. The dipotassium salt of the 2,5-disulfonic acid was synthesized as early as 1899 by Busch and Ziegele<sup>106</sup> by oxidation of the dipotassium salt of "2,5-dimercapto-1,3,4-thiadiazole" with potassium permanganate. In the same way Petri and Glemser<sup>83</sup> prepared 5-hydroxy-2,2'-azo-1,3,4-thiadiazole-5'-sulfonic acid dipotassium salt (**125**) from 2,2'-azo-1,3,4-thiadiazoline-5(4)-thione (**76**).

1,3,4-Thiadiazolesulfonyl chlorides have been the subject of considerable interest as intermediates in the preparation of sulfonamides. They have in general been prepared by oxidative chlorination

<sup>106</sup> M. Busch and E. Ziegele, *J. Prakt. Chem.* [2] **66**, 40 (1899).



of "mercapto-1,3,4-thiadiazoles" or benzylthio-1,3,4-thiadiazoles in aqueous acetic acid,<sup>78, 80</sup> but oxidation of "mercaptothiadiazoles" with iodobenzene dichloride or *tert*-butyl hypochlorite has also been employed.<sup>32</sup> The 2,5-disulfonyl chloride (**126**) has been obtained by oxidative chlorination of "dimercapto-1,3,4-thiadiazole."<sup>107</sup>



1,3,4-Thiadiazole sulfonamides (**127**) have been prepared by treating the sulfochlorides with ammonia in the liquid state or as concentrated aqueous solution.<sup>32</sup>

## 2. Sulfones

These are generally prepared by oxidation of the corresponding sulfides with potassium permanganate, but hydrogen peroxide or chlorine in acetic acid has also been used, though low temperatures are necessary to avoid formation of thiadiazolinones in the latter cases.<sup>92</sup>

# IV. Reactivity

## A. REARRANGEMENTS AND RING-OPENING REACTIONS

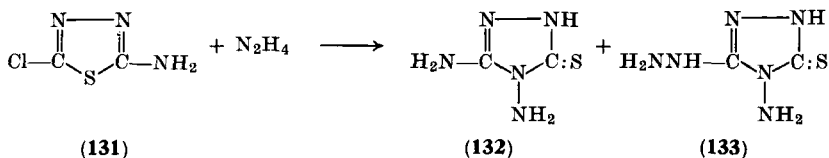
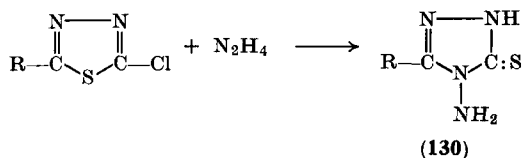
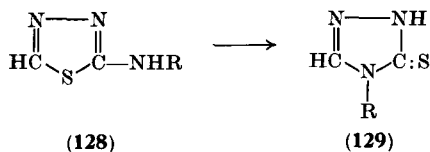
The 1,3,4-thiadiazole ring is rather susceptible to attack by strong nucleophiles. Thus, the parent compound is stable to acids but is readily cleaved by bases.<sup>3</sup> 2-Amino- and 2-hydrazino-1,3,4-thiadiazoles can be rearranged to 1,2,4-triazoline-3(2)-thiones. Goerdeler and Galinke<sup>108</sup> showed that 2-amino- and 2-methylamino-1,3,4-thiadiazole (**128**, R = H and CH<sub>3</sub>) are rearranged by methylamine in methanol at 150° to the isomeric triazolinethiones (**129**). The 5-methyl

<sup>107</sup> U.S. Patent 2,554,816 (1951); *Chem. Abstr.* **46**, 3087 (1952).

<sup>108</sup> J. Goerdeler and J. Galinke, *Chem. Ber.* **90**, 202 (1957).

analog was rearranged in the same way, but refluxing the 5-phenyl analog in sodium ethoxide solution for a long time did not give the corresponding triazolinethione.

2-Amino-1,3,4-thiadiazole (4, R = H), when refluxed with benzylamine in xylene, gave a mixture of about equal amounts of 2-benzylamino-1,3,4-thiadiazole (128, R = CH<sub>2</sub>Ph) and 4-benzyl-1,2,4-tri-

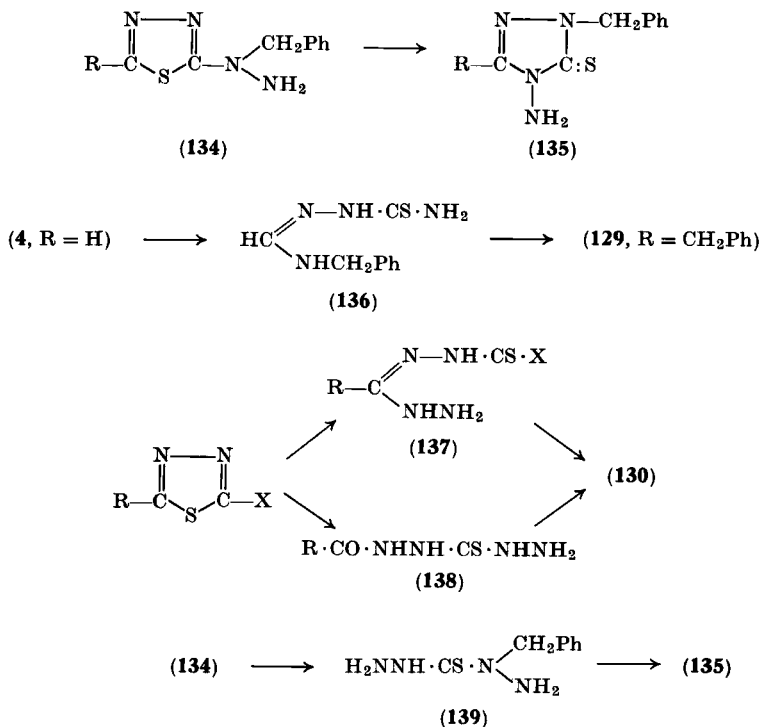


azoline-3(2)-thione (129, R = CH<sub>2</sub>Ph). The same two compounds were formed in the reaction between 2-chloro-1,3,4-thiadiazoles and benzylamine.<sup>61</sup> Similarly, 2-alkyl-5-chloro-1,3,4-thiadiazoles reacted with a large excess (1:5 to 1:10) of hydrazine hydrate on heating to give 4-amino-1,2,4-triazoline-3(2)-thiones (130). Under the same conditions, 2-amino-5-chloro-1,3,4-thiadiazole (131) and 2-amino-1,3,4-thiadiazoline-5(4)-thione (111) gave a mixture of 3,4-diamino-1,2,4-triazoline-5(1)-thione (132) and 3-hydrazino-4-amino-1,2,4-triazoline-5(1)-thione (133). 2,5-Dichloro- and "2,5-dimercapto-1,3,4-thiadiazole" gave only 133.<sup>109</sup>

Similar rearrangements can be effected by acids. When 1-benzyl-1-(1,3,4-thiadiazol-2-yl)hydrazine (134) was refluxed with dilute hydrochloric acid, the triazolinethione (135, R = H) was formed in

<sup>109</sup> H. Saikachi and M. Kanaoka. *Yakugaku Zasshi* **82**, 683 (1962); *Chem. Abstr.* **58**, 4543 (1963).

quantitative yield. When the reaction was performed in the presence of some acetic acid, a mixture of **135** ( $R = H$ ) and **135** ( $R = CH_3$ ) was formed.<sup>89</sup>



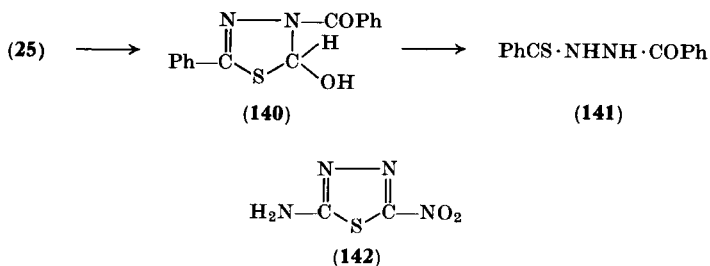
The rearrangement of **4** by benzylamine probably proceeds with ring-opening to an amidrazone (**136**) followed by recyclization to **129** ( $R = CH_2Ph$ ). The rearrangements in hydrazine hydrate may proceed with hydrazidines (**137**) or acylthiohydrazides (**138**) as intermediates. X indicates a labile substituent, R an alkyl or amino group. The formation of **133** necessitates a more far-reaching degradation, and possibly thiocarbohydrazide is an intermediate.

In the acid-catalyzed rearrangement mentioned above, 2-benzylthiocarbohydrazide (**139**) is a likely intermediate. Beyer and Kröger<sup>62</sup> have shown that thiocarbohydrazide is cyclized in good yield to **130** by carboxylic acids.

The preferential formation of triazolinethiones is in agreement with the results of molecular orbital calculations, which predict a larger

$\pi$ -electron stabilization for the system **129** ( $R=H$ ) than for **128** ( $R=H$ ).<sup>89</sup>

Bacchetti<sup>41</sup> has observed three new cleavages of the 1,3,4-thiadiazole ring. 2-Chloro-5-phenyl-1,3,4-thiadiazole was decomposed by



magnesium to benzonitrile and rhodanide ion in 60% yield. A similar reaction occurred when 2-benzoyl-5-phenyl-1,3,4-thiadiazole (**26**) reacted with sodium ethoxide in aprotic solvents. The 2-phenyl-1,3,4-thiadiazol-5-yl anion is proposed as an intermediate. The third reaction shows that the susceptibility of the 1,3,4-thiadiazole ring to nucleophiles is increased by quaternization. Thus 2-phenyl-1,3,4-thiadiazole with benzoyl chloride gave the 4-benzoylthiadiazolium ion (**25**), which was decomposed by bases to 1-benzoyl-2-thiobenzoylhydrazine (**141**), probably with the pseudo base (**140**) as an intermediate.

Sodium amalgam reduced 2-amino-5-phenyl-1,3,4-thiadiazole (**38**) to benzaldehyde thiosemicarbazone, whereas the 5-H and 5-methyl analogs were unaffected. The latter compounds could not be reduced polarographically, whereas **38** gave a half wave potential of  $-1.940$  volts.<sup>110</sup>

## B. SUBSTITUTION REACTIONS

Although the 1,3,4-thiadiazole ring is classed as  $\pi$ -excessive according to Albert,<sup>111</sup> the presence of two nitrogen atoms of pyridine type in the ring leaves the carbon atoms with rather low electron density, and consequently no electrophilic substitutions in the unsubstituted

<sup>110</sup> F. F. Medovshchikova and I. Ya. Postovskii, *J. Gen. Chem. USSR (English Transl.)* **24**, 1989 (1954).

<sup>111</sup> A. Albert, "Heterocyclic Chemistry," Oxford Univ. Press (Athlone), London and New York, 1959.

1,3,4-thiadiazole ring have been recorded. Goerdeler *et al.*<sup>3</sup> obtained a bromine adduct of the simple 1,3,4-thiadiazole, but it decomposed and lost bromine in the air. Nitration, even under drastic conditions, could not be achieved.

Ohta *et al.*<sup>9</sup> subjected 2-phenyl-1,3,4-thiadiazole to a mixture of concentrated nitric and sulfuric acids at 0° and obtained a mixture of the three isomeric 2-nitrophenyl-1,3,4-thiadiazoles in the ratio *p:m:o* = 2:3:1, but no 2-phenyl-5-nitro-1,3,4-thiadiazole. The products were identified by oxidation to the corresponding nitrobenzoic acids.

A patent<sup>112</sup> describes the preparation of 2-amino-5-nitro-1,3,4-thiadiazole (**142**) by nitration of 2-amino-1,3,4-thiadiazole (**4**, R = H) with fuming nitric acid at 40°. However, the product has the same melting point as the 2-nitramino-1,3,4-thiadiazole (**46**, R = H) described by Kanaoka,<sup>28</sup> which was obtained under very similar conditions. Since the structure of **46** (R = H) was demonstrated by reduction to 2-hydrazino-1,3,4-thiadiazole, the structure **142** may be viewed with some skepticism.

However, a 2-amino group does activate the ring towards electrophilic agents, since Bak *et al.*<sup>5</sup> could prepare 2-amino-5-bromo-1,3,4-thiadiazole by bromination of 2-amino-1,3,4-thiadiazole in 40% hydrobromic acid. The product was not isolated but was diazotized *in situ* to give 2,5-dibromo-1,3,4-thiadiazole.

As has been mentioned previously, the reactivity of halogeno- and methylsulfonyl-1,3,4-thiadiazoles toward nucleophilic reagents is in agreement with the low electron density on the carbon atoms in the ring. The high coupling activity of the diazonium salts can be ascribed to the same cause.

Bacchetti *et al.*<sup>112a</sup> have investigated the kinetics of the nucleophilic substitution of 2-aryl-5-chloro-1,3,4-thiadiazoles with piperidine in ethanol and benzene. In ethanol, the reaction was first order in both components, whereas in benzene it was pseudo-first order in thiadiazole, but intermediate between first and second order in piperidine, indicating intervention of associated amine molecules in the substitution. The logarithms of the rate constants from ethanol gave an excellent Hammett plot against the  $\sigma$  values for the para substituents in the phenyl ring.

<sup>112</sup> U.S. Patent 2,790,791 (1957); *Chem. Abstr.* **51**, 13402 (1957).

<sup>112a</sup> A. Alemagna, T. Bacchetti, and P. Beltrame, *Tetrahedron*, in press.

These results have made possible a comparison of the reactivities of the chlorine atoms in 3-phenyl-5-chloro-1,2,4-thiadiazole, 2-phenyl-5-chloro-1,3,4-thiadiazole, and 3-chloro-5-phenyl-1,2,4-thiadiazole. The reaction of the first and last compound with piperidine in ethanol has been investigated by Goerdeler and Heller,<sup>112b</sup> and the rate constants of the three compounds at 30° decrease in the ratio 7000:64:1. This order is the same as has been predicted by Zahradník and Koutecký<sup>113</sup> on the basis of localization energies for the nucleophilic reactivity of the simple ring systems.

## V. Physical Properties

### A. STRUCTURE, AROMATIC PROPERTIES, AND DIPOLE MOMENT

Bak *et al.*<sup>114</sup> recently made a careful analysis of the microwave spectra of 1,3,4-thiadiazole and three isotopically substituted species. They could determine the structure of the molecule with an uncertainty of 0.03 Å in the coordinates of the hydrogen atoms and of less

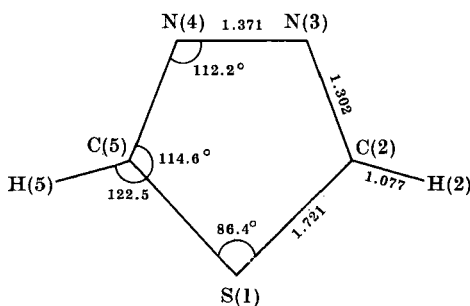


FIG. 1. Bond lengths and angles in 1,3,4-thiadiazole, from B. Bak, L. Nygaard, E. J. Pedersen, and J. Rastrup-Andersen, *J. Mol. Spectr.* **19**, 283 (1966).

than 0.003 Å in the coordinates of the other atoms (Fig. 1). By an analysis of differences between the measured bond lengths and covalent radii, the authors came to the conclusion that the aromatic character, as measured by the  $\pi$ -electron delocalization, decreases in the order 1,2,5-thiadiazole > thiophene > 1,3,4-thiadiazole > 1,2,5-oxadiazole.

<sup>112b</sup> J. Goerdeler and K. H. Heller, *Chem. Ber.* **97**, 225 (1964).

<sup>113</sup> R. Zahradník and J. Koutecký, *Collection Czech. Chem. Commun.* **26**, 156 (1961).

<sup>114</sup> B. Bak, L. Nygaard, E. J. Pedersen, and J. Rastrup-Andersen, *J. Mol. Spectr.* **19**, 283 (1966).

Zahradník and Koutecký<sup>113</sup> made a series of molecular orbital calculations by the HMO method, using the Longuet-Higgins model for the sulfur atom,<sup>115</sup> on thiazole and the isomeric thiadiazoles. They found the largest  $\pi$ -electron stabilization for the 1,2,4 isomer, but very little difference between the 1,2,5 and 1,3,4 isomers. The calculated bond orders, however, show a larger  $\pi$ -electron delocalization in the 1,2,5 than in the 1,3,4 isomer, in agreement with the results of Bak *et al.*<sup>114</sup> The formal double bonds have a lower bond order in the 1,2,5 than in the 1,3,4 isomer, whereas the reverse is true for the formal single bonds. These relations hold for three different sets of parameters for the carbon-sulfur bond.

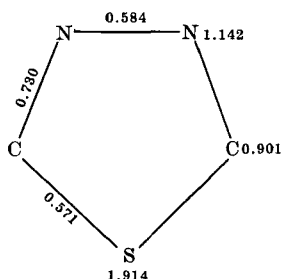


FIG. 2.  $\pi$ -Electron distribution and bond orders in 1,3,4-thiadiazole from R. Zahradník and J. Koutecký [*Collection Czech. Chem. Commun.* **26**, 156 (1961)] ( $x_{\text{cs}} = 0.8$ ).

Bak *et al.*<sup>116</sup> measured the dipole moment of 1,3,4-thiadiazole in the gas phase by microwave technique and found a value of  $3.28 \pm 0.03$  D. By use of the geometry of Bak *et al.*<sup>114</sup> the  $\pi$ -electron distribution of Zahradník and Koutecký<sup>113</sup> ( $x_{\text{cs}} = 0.8$ , Fig. 2), and the bond moments of Smith,<sup>117</sup> a dipole moment of 3.0 D can be calculated, directed from the sulfur atom toward the center of the nitrogen-nitrogen bond.

## B. SPECTRA AND PK VALUES

The ultraviolet absorption spectra of 1,3,4-thiadiazole derivatives have mostly been recorded in connection with studies of tautomeric equilibria, which means that the interest has been centered on

<sup>115</sup> H. C. Longuet-Higgins, *Trans. Faraday Soc.* **45**, 173 (1949).

<sup>116</sup> B. Bak, D. Christensen, L. Hansen-Nygaard, L. Lipschitz, and J. Rastrup-Andersen, *J. Mol. Spectr.* **9**, 225 (1962).

<sup>117</sup> J. W. Smith, "Electric Dipole Moments," pp. 92 and 94. Butterworth, London and Washington, D.C., 1955.

functional derivatives. No large systematic study has been performed, but data from different sources have been collected in Table I.

The unconjugated 1,3,4-thiadiazoles, like **6** ( $R = H$  and  $CH_3$ ), show no selective absorption above 220 nm ( $R = H$ )<sup>3</sup> and 230 nm ( $R = CH_3$ ),<sup>118</sup> respectively. 1,2,4-Thiadiazole, on the other hand, has a

TABLE I  
ULTRAVIOLET SPECTRA OF 1,3,4-THIADIAZOLES

$R_2$	$R_4$	$R_5$	Solvent	$\lambda_{\max}$ (nm)	$\log \epsilon$	Reference
$CH_3$	—	$NH_2$	Water	252	3.7	<i>a</i>
$CH_3$	—	$SCH_3$	Ethanol	269	3.94	<i>b</i>
$PhCH_2S$	—	$NH_2$	Dioxan	281	3.96	<i>c</i>
Ph	—	H	Ethanol	268	4.12	<i>d</i>
<i>p</i> - $O_2N \cdot C_6H_4$	—	H	Ethanol	291	4.20	<i>d</i>
<i>m</i> - $O_2N \cdot C_6H_4$	—	H	Ethanol	258	4.22	<i>d</i>
<i>o</i> - $O_2N \cdot C_6H_4$	—	H	Ethanol	No maximum	—	<i>d</i>
Ph	—	Ph	Ethanol	302	4.1	<i>e</i>
Ph	—	$NH_2$	Water	295	4.15	<i>f</i>
Ph	—	$SCH_3$	Ethanol	301	4.20	<i>b</i>
$PhCH_2S$	—	$PhCH_2S$	Dioxan	292	4.10	<i>c</i>
$CH_3$	H	:S	Ethanol	309	4.14	<i>b</i>
$CH_3S$	H	:S	Dioxan	323	4.19	<i>c</i>
Ph	H	:S	Ethanol	337	4.27	<i>b</i>
Ph	$C_2H_5$	:NH	Water	315	4.06	<i>f</i>

<sup>a</sup> J. Goerdeler, *Chem. Ber.* **87**, 57 (1954).

<sup>b</sup> J. Sandström and I. Wennerbeck, *Acta Chem. Scand.* **20**, 57 (1966).

<sup>c</sup> N. Petri and O. Glemser, *Chem. Ber.* **94**, 566 (1961).

<sup>d</sup> M. Ohta, R. Hagiwara, and Y. Mizushima, *J. Pharm. Soc. Japan* **73**, 701 (1953); *Chem. Abstr.* **48**, 7005 (1954).

<sup>e</sup> P. Grammaticakis, *Bull. Soc. Chim. France*, p. 86 (1953).

<sup>f</sup> E. Testa, G. G. Gallo, F. Fava, and G. Weber, *Gazz. Chim. Ital.* **88**, 812 (1958).

$\pi \rightarrow \pi^*$  maximum at 229 nm.<sup>3</sup> In agreement with this, Zahradník and Kouřeký<sup>113</sup> calculated a larger transition energy for 1,3,4-thiadiazole than for 1,2,4-thiadiazole.

As in other heteroaromatic systems, substituents with lone pairs cause bathochromic shifts, and the effect of such substituents seems to be very roughly additive when they appear both in positions 2 and 5. It is of interest to note that the effect of an alkylthio group is larger than that of an amino group. This is in agreement with the electron-attracting character of the ring carbon atoms, which can cause a

<sup>118</sup> P. Grammaticakis, *Bull. Soc. Chim. France*, 86 (1953).



contraction of the polarizable  $3p$  orbital of the substituent sulfur atom and thus improve the overlap between this orbital and the  $\pi$  orbitals of the ring.

A phenyl group in position 2 causes a considerable bathochromic shift, which is increased by a  $p$ -nitro group, obviously due to the extension of the delocalized system. On the other hand an  $m$ -nitro group causes a hypsochromic shift. In this case the inductive effect dominates, and  $-I$  effects in general seem to be hypsochromic. The spectrum of 2- $o$ -nitrophenyl-1,3,4-thiadiazole shows only end absorption above 220 nm, probably due to a strong steric hindrance to coplanarity.<sup>9</sup>

1,3,4-Thiadiazoline-5(4)-thiones **5**, ( $R = :S$ ) absorb at rather long wavelength, but molecular orbital calculations<sup>104</sup> indicate that these compounds are more like conjugated thioamides than heteroaromatic compounds.

Grammaticakis<sup>118</sup> has found that the sulfur atom in the ring has a considerable bathochromic effect compared to oxygen. In a series of simple 1,2-diazoles, the bathochromic effect of the third hetero atom was found to increase in the order nitrogen < oxygen < sulfur, in agreement with the results of molecular orbital calculations.<sup>104</sup>

The infrared spectrum of 1,3,4-thiadiazole has been recorded by Goerdeler *et al.*<sup>3</sup> and by Bak *et al.*<sup>5</sup> A slight divergency from the earlier spectrum was recorded by the latter group. A complete assignment of the vibration bands of gaseous, dissolved, and solid 1,3,4-thiadiazole has been given by Sbrane and Ginanneschi.<sup>118a</sup> On the basis of this work, Soptrajanov<sup>118b</sup> has calculated the thermodynamic functions for 1,3,4-thiadiazole and compared them with those of 1,2,5-thiadiazole and its  $d_2$  analog. No systematic study of the infrared spectra of 1,3,4-thiadiazoles seems to have been performed. The technique has frequently been used in studies of tautomeric equilibria, e.g., to ascertain the presence of a carbonyl group, but generally only a few individual band positions have been recorded.

The nmr spectrum of 1,3,4-thiadiazole has been recorded in chloroform solution.<sup>5</sup> It showed a single signal at  $\tau = 0.62$ , in agreement with the low electron density of the carbon atoms.

<sup>118a</sup> G. Sbrane and M. Ginanneschi, *Spectrochim. Acta* **22**, 517 (1966).

<sup>118b</sup> B. Soptrajanov, *Croat. Chem. Acta* **39**, 27 (1967).

TABLE II  
pK<sub>a</sub> VALUES OF CONJUGATE ACIDS OF AMINO- AND  
IMINO-1,3,4-THIADIAZOLES

R <sub>2</sub>	R <sub>4</sub>	R <sub>5</sub>	pK <sub>H+</sub>	Reference
H	—	NHPh	1.76	<i>a</i>
H	—	NCH <sub>3</sub> Ph	2.24	<i>a</i>
H	CH <sub>3</sub>	:NPh	4.56	<i>a'</i>
Ph	—	NH <sub>2</sub>	2.9	<i>b</i>
Ph	—	NHCH <sub>3</sub>	2.8	<i>c</i>
Ph	C <sub>2</sub> H <sub>5</sub>	:NH	7.9	<i>b</i>
Ph	—	NHPh	1.79	<i>d</i>
Ph	—	NCH <sub>3</sub> Ph	2.10	<i>d</i>
Ph	CH <sub>3</sub>	:NPh	4.14	<i>d</i>

<sup>a</sup> J. Menin, J.-F. Giudicelli, and H. Najer, *Compt. Rend.* **261**, 766 (1965).

<sup>b</sup> E. Testa, G. G. Gallo, F. Fava, and G. Weber, *Gazz. Chim. Ital.* **88**, 812 (1958).

<sup>c</sup> E. Testa, G. G. Gallo, and F. Fava, *Gazz. Chim. Ital.* **88**, 1272 (1958).

<sup>d</sup> J. Menin, J.-F. Giudicelli, and H. Najer, *Compt. Rend.* **259**, 3563 (1964).

TABLE III  
pK<sub>a</sub> AND pK<sub>H+</sub> VALUES OF ACIDIC 1,3,4-THIADIAZOLE DERIVATIVES

R <sub>2</sub>	R <sub>4</sub>	R <sub>5</sub>	pK <sub>H+</sub>	pK <sub>a1</sub>	pK <sub>a2</sub>	Reference
CH <sub>3</sub>	H	:S	—	4.90	—	<i>a</i>
Ph	H	:S	—	4.98	—	<i>a</i>
HS	H	:S	-5.40	-1.36	7.53	<i>b</i>
HS	CH <sub>3</sub>	:S	-5.30	-1.40	—	<i>b</i>
HS	Ph	:S	-6.50	-1.59	—	<i>b</i>
CH <sub>3</sub> S	H	:S	-4.85 <sup>b</sup>	5.20 <sup>c</sup>	—	
CH <sub>3</sub> S	Ph	:S	-5.44	—	—	<i>b</i>
H	—	NHN:C(CH <sub>3</sub> ) <sub>2</sub>	—	10.8	—	<i>d</i>
CH <sub>3</sub> S	—	NHN:C(CH <sub>3</sub> ) <sub>2</sub>	—	10.5	—	<i>d</i>
Ph	—	NHN:C(CH <sub>3</sub> ) <sub>2</sub>	—	10.7	—	<i>d</i>
Ph	—	NHCOCH <sub>3</sub>	—	8.9	—	<i>e</i>
Ph	—	NHCOPh	—	6.8	—	<i>e</i>

<sup>a</sup> J. Sandström and I. Wennerbeck, *Acta Chem. Scand.* **20**, 57 (1966).

<sup>b</sup> B. Stanovnik and M. Tišler, *Croat. Chem. Acta* **37**, 17 (1965).

<sup>c</sup> J. Sandström, unpublished results (1961).

<sup>d</sup> J. Sandström, *Acta Chem. Scand.* **18**, 871 (1964).

<sup>e</sup> E. Testa, G. G. Gallo, and F. Fava, *Gazz. Chim. Ital.* **88**, 1272 (1958).

The unsubstituted 1,3,4-thiadiazole is sufficiently basic to give a stable hydrochloride and hydrobromide, but it is described as very weakly basic,<sup>3</sup> though no  $pK_a$  value has been published. 2-Amino- and 2-anilino-1,3,4-thiadiazoles are also weak bases, whereas the tautomeric imines are somewhat stronger.  $pK$  values have been useful in tautomerism studies, and some  $pK_{H^+}$  values, i.e.,  $pK_a$  values of the conjugate acids, have been collected in Table II and will be discussed in the following section.

Due to the electron attraction of the ring, the NH groups in amidothiadiazoles and thiadiazolylhydrazones (54) have weakly acidic character. Potential mercapto compounds have distinctly acidic properties, and "2,5-dimercapto-1,3,4-thiadiazole" and its 4-substituted derivatives are strong acids. The  $pK_a$  and some  $pK_{H^+}$  values of these compounds are found in Table III.

#### C. PROTOTROPIC TAUTOMERISM OF AMINO-, HYDROXY-, AND MERCAPTO-1,3,4-THIADIAZOLES

This field has been reviewed in Volume 2 of this series,<sup>119</sup> and therefore mostly more recent work will be discussed.

Das and Rout<sup>120</sup> claim to have prepared the imino forms (143) of several 2-toluidino-1,3,4-thiadiazoles (145) by oxidation of the corresponding 4-tolylthiosemicarbazones (144) with iodine or potassium ferricyanide in alkaline solution. Later, Ramachander and Srinivasan<sup>121, 122</sup> repeated this synthesis in similar systems, but they also prepared the tautomers (145) by oxidation of 144 with ferric chloride. It is highly unlikely that individual tautomers like 143 and 145 should exist as separate compounds, particularly as they have crystallized from the same solvent, ethanol. The only proofs for the structure 143 are sulfur analyses, but it is evident from the melting points that 143 is identical neither with 145 nor with the isomeric triazolinethiones. Menin *et al.*<sup>50</sup> tried to repeat the preparation of 143, though without success.

The French authors studied the tautomeric equilibrium of 2-anilino-5-phenyl-1,3,4-thiadiazole (42). They prepared the two *N*-methyl derivatives (146 and 147) corresponding to the individual

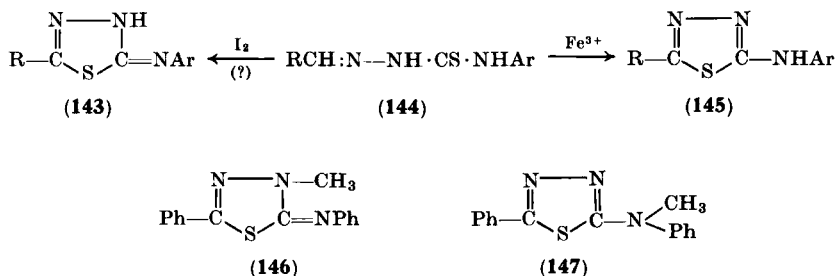
<sup>119</sup> A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.* **2**, 27 (1963).

<sup>120</sup> K. C. Das and M. K. Rout, *J. Sci. Ind. Res. (India)* **14B**, 98 (1955).

<sup>121</sup> G. Ramachander and V. R. Srinivasan, *J. Sci. Ind. Res. (India)* **21C**, 44 (1962).

<sup>122</sup> V. R. Srinivasan and G. Ramachander, *Indian J. Chem.* **1**, 234 (1963).

tautomers. The ultraviolet and infrared spectra of **146** and **147** were not sufficiently different to allow a conclusion regarding the position of the equilibrium between the tautomers. The  $pK_a$  values (Table II) were interpreted to show that the equilibrium is on the side of the amino form. The estimation of tautomeric equilibrium constants from  $pK$  constants<sup>123</sup> requires that **146** adds a proton to the nitrogen atom 3, and **147** to the exocyclic nitrogen atom, and that neither of them is



appreciably protonated on nitrogen atom 4. This assumption does not seem unreasonable, since the amidine part of the molecule can be expected to be the center of basicity. Molecular orbital calculations on 2-amino-1,3,4-thiadiazole and the corresponding imine place the highest negative charge on nitrogen atom 3 in the amine and on the exocyclic nitrogen atom in the imine.<sup>124</sup> Still, the *N*-phenyl group may change the picture, and the tautomeric constant estimated from  $pK_a$  values is uncertain, as long as the site of protonation is not firmly established.

In a later work Menin *et al.*<sup>125</sup> studied the tautomeric equilibrium in 2-anilino-1,3,4-thiadiazole (**148a,b**), which had earlier been investigated by Stanovnik and Tišler.<sup>56</sup> However, the compound used by the latter authors as a model for the imino form (**148b**), and prepared by reaction between 2-methyl-4-phenylthiosemicarbazide and triethyl orthoformate, is claimed by Menin *et al.*<sup>125</sup> to be the isomeric triazolinethione (**149**).<sup>126</sup> They prepared the authentic 2-phenylimino-3-methyl-1,3,4-thiadiazoline (**151**) by oxidation of glyoxylic acid 2-methyl-4-phenylthiosemicarbazide (**150**) with ferric chloride. The properties of the latter product (basicity, low melting point) are said

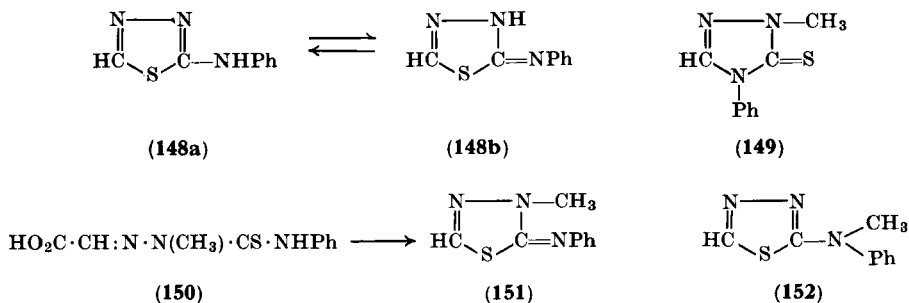
<sup>123</sup> A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.* **1**, 311 (1963).

<sup>124</sup> J. Sandström, *Acta Chem. Scand.* **18**, 871 (1964).

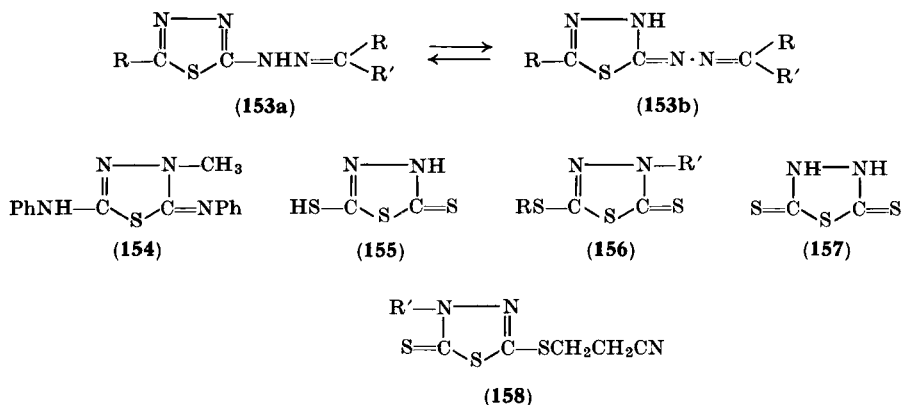
<sup>125</sup> J. Menin, J.-F. Giudicelli, and H. Najer, *Compt. Rend.* **261**, 766 (1965).

<sup>126</sup> This compound was erroneously given a "mesoionic" formulation.

to agree much better with the expected structure than those of the compound described in Stanovnik and Tišler.<sup>56</sup> For 2-(*N*-methyl-anilino)-1,3,4-thiadiazole (**152**), used as model for (**148a**), the two groups obtained identical data. The ultraviolet and infrared spectra



of **148**, **151**, and **152** are too similar to give information about the position of the equilibrium between **148a** and **148b**. The  $\text{pK}_a$  values (Table II), with the same reservations as in the previous case, indicate that the amino form is the more stable one.



For thiadiazolyhydrazones (**153a,b**), the two *N*-methyl models have much more different ultraviolet spectra, and it can be safely concluded that the hydrazone form (**153a**) dominates strongly over the azine form (**153b**). This is also in agreement with the results of molecular orbital calculations, which predict a considerably larger  $\pi$ -electron stabilization for **153a** than for **153b**. The same relation has

been found between the 2-amino and 2-imino forms of 1,3,4-thiadiazole, thiazole, and pyridine, and also between the 4-amino and 4-imino forms of pyridine.<sup>124</sup>

No thorough study of the tautomerism of any 2,5-diamino-1,3,4-thiadiazole derivatives seems to have been made, but Stanovnik and Tišler<sup>70</sup> observed that 2,5-dianilino-1,3,4-thiadiazole (**60**) and 2-anilino-4-methyl-5(4)-phenylimino-1,3,4-thiadiazole (**154**) have rather similar ultraviolet spectra, which was taken as an indication that **60** might exist predominantly in the monoimino form. Much more work on this system is needed, though, before a safe conclusion can be reached.

Potential 2-hydroxy- and 2-mercapto-1,3,4-thiadiazoles have been examined both by infrared and by ultraviolet spectra in the solid state and in solution by Sheinker *et al.*<sup>127</sup> They concluded that these compounds exist in the 2-oxo and 2-thione forms, respectively. To "2,5-dimercapto-1,3,4-thiadiazole" the 2-mercapto-5-thione structure (**155**) was given. The structure of this compound has been the subject of some controversy.<sup>119</sup> Stanovnik and Tišler<sup>128</sup> have added some valuable arguments to the discussion. They measured the  $pK_a$  values of **155**, its *N*-methyl, *N*-phenyl, and *N*-phenyl-*S*-methyl derivatives (**156**), and of the conjugate acids of these and the *S*-methyl derivative ( $pK_H^+$ ) (Table III). In all compounds **156** with  $R = H$ , the infrared spectrum showed an absorption band near  $2300\text{ cm}^{-1}$  characteristic of the SH group. They also had  $pK_{a1}$  values near  $-1.5$ , which in connection with the infrared evidence was taken as characteristic of an SH group in this situation. Since the 2,5-dithiol structure is excluded by ultraviolet spectral evidence,<sup>129</sup> the 2-mercapto-5-thione structure (**155**) seems rather well established. It has previously been shown by Thorn<sup>129</sup> to predominate in chloroform solution, whereas he concluded that the dithione form (**157**) should predominate in ethanol solution. However, the  $pK_{a1}$  value for **155**,  $-1.36$ , makes it rather probable that Thorn used the monoanion of **155** instead of the acid itself for spectral comparison, and in that case his conclusions have a very weak foundation.

Stanovnik and Tišler<sup>128</sup> also observed that **155** and **156** ( $R = H$ ) underwent cyanoethylation by acrylonitrile on a thiol group to give

<sup>127</sup> Yu. N. Sheinker, I. Ya. Postovskii, and N. M. Voronina, *Zh. Fiz. Khim.* **33**, 302 (1959); *Chem. Abstr.* **54**, 4147 (1960).

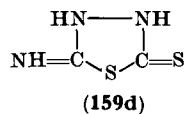
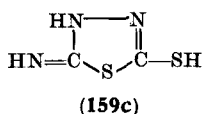
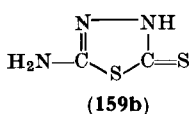
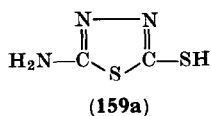
<sup>128</sup> B. Stanovnik and M. Tišler, *Croat. Chem. Acta* **37**, 17 (1965).

<sup>129</sup> G. D. Thorn, *Can. J. Chem.* **38**, 1439 (1960).

2- $\beta$ -cyanoethylthio-1,3,4-thiadiazoline-5(4)-thiones (158), whereas with thioamides and also "monomercapto-1,3,4-thiadiazoles" addition to nitrogen is the rule. Though in general the structures of reaction products are poor guides to chemical equilibria, the above results are of interest in connection with the demonstrated preponderance of the thionethiol form (155).

2-Methyl- and 2-phenyl-1,3,4-"thiadiazole-5-thiol" have been shown by comparing the ultraviolet spectra of the free acids with those of their *N*- and *S*-methyl derivatives to be mainly in the thione form. Molecular orbital calculations support these results, since they predict a larger  $\pi$ -electron stabilization for the thione than for the thiol forms.<sup>104</sup>

Petri<sup>130</sup> investigated the ultraviolet spectra of "2-amino-5-mercapto-1,3,4-thiadiazole" (111) and some model compounds. For



111 four combinations (159a-d) of thiol, thione, amino, and imino form are possible. Petri came to the conclusion that the aminothione form (159b) predominates, but he did not use spectra of model compounds in which no tautomeric changes are possible. Even if his result seems likely, it cannot be regarded as firmly established.

## VI. Uses

As mentioned in the introduction, sulfonamides derived from 1,3,4-thiadiazoles directed interest on this ring system. The first compounds were 5-substituted 2-sulfanilamido-1,3,4-thiadiazoles, but later 1,3,4-thiadiazole-2-sulfonamides came into focus due to the discovery by Miller *et al.*<sup>131</sup> of the carbonic anhydrase inhibiting effect of 2-acetamido-1,3,4-thiadiazole-5-sulfonamide. Under the names of diamox and acetazolamide this compound has been extensively investigated for its effect on salt excretion and eye pressure, and

<sup>130</sup> N. Petri, *Z. Naturforsch.* **17b**, 278 (1962).

<sup>131</sup> W. H. Miller, A. M. Dessert, and R. O. Roblin, Jr., *J. Am. Chem. Soc.* **72**, 4893 (1950).

also as an anticonvulsive agent.<sup>132</sup> Other 1,3,4-thiadiazoles have been tried as chemotherapeutics, and 2-amino-5-(2-nitro-5-furyl)-1,3,4-thiadiazole<sup>133</sup> and some of its derivatives showed considerable promise as remedies for infections in the gastrointestinal tract.

Krasovitskii *et al.*<sup>134</sup> prepared useful azo dyes by coupling bis-diazotized 2,5-bis(4-aminophenyl)-1,3,4-thiadiazole with aminonaphtholdisulfonic acids.

"2,5-Dimercapto-1,3,4-thiadiazole" has been used as a reagent for photometric determination of metals under the name of Bismuthiol I.<sup>135</sup> It has also, like several of its *S*-substituted derivatives, been used as a herbicide.<sup>136</sup>

Miscellaneous uses of 1,3,4-thiadiazoles, such as corrosion inhibition, vulcanization acceleration, and prevention of sunburn and darkening of photographic developers are recorded in the patent literature.

<sup>132</sup> E. Gores, G. Hilgetag, and F. Jung, *Acta Physiol. Acad. Sci. Hung.* **19**, 95 (1961).

<sup>133</sup> K. Skagius and B. Zetterberg, *Antibiot. Chemotherapy* **9**, 37 (1961).

<sup>134</sup> B. M. Krasovitskii, R. M. Matskevich, N. S. Dokunikhin, and N. A. Trubitsyna, *J. Gen. Chem. USSR (English Transl.)* **30**, 2589 (1960).

<sup>135</sup> A. K. Majumdar and M. M. Chakrabartty, *Anal. Chim. Acta* **19**, 372 (1958).

<sup>136</sup> German Patent 964,548 (1957); *Chem. Abstr.* **54**, 3840 (1960).



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# Pyridazines

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## I. Introduction

Although the first pyridazines were obtained as early as 1886 by Fischer,<sup>1</sup> major attention has been devoted to their chemistry only in the past two decades. One reason why pyridazines were not investigated as thoroughly as other diazines is that pyridazines do not occur as natural products. Since they contain a potential hydrazine unit in the ring, they are not readily obtainable from biochemical

<sup>1</sup> E. Fischer, *Ann. Chem.* **236**, 147 (1886).

transformations involving nitrogen. However, pyridazines have recently received much more attention from the theoretical standpoint and, since many derivatives were found to possess potential therapeutic or plant growth inhibitory effect, many new syntheses have been developed.

The chemical literature contains many articles reporting the reactions and properties of pyridazines, but there are relatively few reviews within narrow limits.<sup>2-8</sup> The most comprehensive was presented by Jacobs<sup>9</sup> in 1957.

The scope of the present review is to summarize the chemistry of pyridazines, taking into account recent developments and involving chemical principles rather than attempting to give an encyclopedic coverage of this field. Literature data are covered until November 1966.

Throughout this review, the nomenclature is based upon the current usage of *Chemical Abstracts* and therefore some names may be different from those in the original papers.

## II. Pyridazine

Pyridazine, one of three possible isomeric diazines, can be regarded as a cyclic hydrazone and the mutual proximity of the nitrogen atoms is reflected in somewhat different properties and reactions when compared to those of pyrimidine and pyrazine.

Pyridazine was first synthesized by Täuber,<sup>10</sup> who oxidized benzo[c]cinnoline to 3,4,5,6-pyridazinetetracarboxylic acid which was subsequently decarboxylated. All other syntheses of pyridazine, however, involve nuclear synthesis and are in the main cumbersome and characterized by poor yields. The reaction between a 1,4-ketoacid

<sup>2</sup> J. Druey, *Angew. Chem.* **70**, 5 (1958).

<sup>3</sup> K. Dury, *Angew. Chem.* **77**, 282 (1965).

<sup>4</sup> J. Druey, *Pharm. Acta Helv.* **38**, 193 (1963).

<sup>5</sup> C. G. Wermuth, *Agressologie* **6**, 383 (1965).

<sup>6</sup> J. Kokosinski and A. Jankowska, *Przemysl Chem.* **45**, 400 (1966).

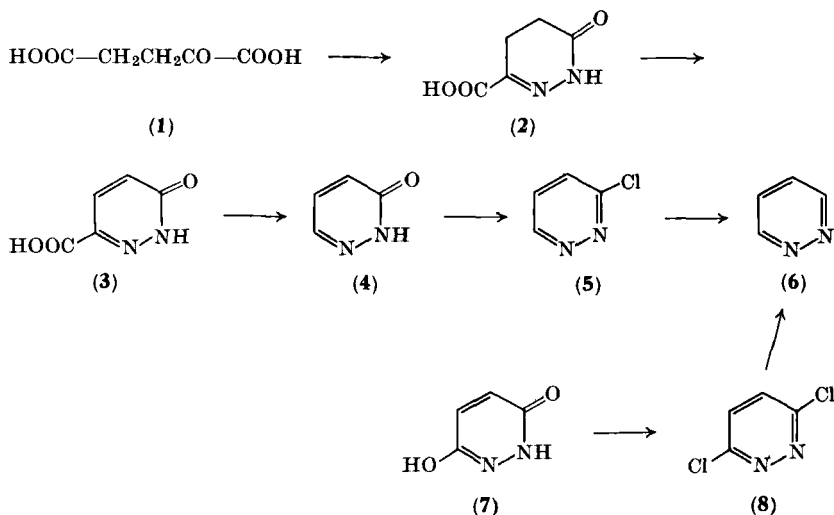
<sup>7</sup> T. Imai, *Eisei Shikensho Hokoku* **82**, 1 (1964); *Chem. Abstr.* **65**, 8901 (1966).

<sup>8</sup> E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IV, Part B, p. 1201. Elsevier, Amsterdam, 1959.

<sup>9</sup> T. L. Jacobs, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, p. 101. Wiley, New York, 1957.

<sup>10</sup> E. Täuber, *Chem. Ber.* **28**, 451 (1895).

and hydrazine to form the pyridazinone,<sup>11</sup> in particular from  $\alpha$ -ketoglutaric acid (1) (yield 24%)<sup>12</sup> was formerly the preferred procedure. The lengthy multistep synthesis was modified and the yield was improved.<sup>13</sup>



Other syntheses involve the preparation from the monoacetate of the enolic form of nitrosuccindialdehyde,<sup>14</sup> or the dibenzoyldioxime of maleic aldehyde,<sup>15</sup> or by dehydrogenation of 1-tosyl-1,4-dihydropyridazine.<sup>16</sup> From 2,5-diacetoxy-<sup>17</sup> or 2,5-dimethoxy-2,5-dihydrofuran<sup>18</sup> pyridazine can be obtained in high yield. Maleic aldehyde has been obtained also when decomposing the adduct obtained in the Diels-Alder reaction between furan and diethyl azodicarboxylate and straightforward condensation with hydrazine afforded pyridazine in 55% yield.<sup>19</sup> Another direct reaction involving maleic aldehyde

<sup>11</sup> S. Gabriel and J. Colman, *Chem. Ber.* **32**, 395 (1899).

<sup>12</sup> S. Gabriel, *Chem. Ber.* **42**, 654 (1909).

<sup>13</sup> R. C. Evans and F. Y. Wiselogle, *J. Am. Chem. Soc.* **67**, 60 (1945).

<sup>14</sup> R. Marquis, *Compt. Rend.* **136**, 368 (1903).

<sup>15</sup> R. Marquis, *Ann. Chim. Phys.* [8] **4**, 196 (1905).

<sup>16</sup> D. Lemal and T. W. Rave, *Tetrahedron* **19**, 1119 (1963).

<sup>17</sup> N. Clauson-Kaas, Si-Oh Li, and N. Elming, *Acta Chem. Scand.* **4**, 1233 (1950).

<sup>18</sup> R. Letsinger and R. Lasco, *J. Org. Chem.* **21**, 764 (1956).

<sup>19</sup> K. N. Zelenin and I. P. Bežan, *Zh. Organ. Khim.* **2**, 1524 (1966).

tetraacetal gives pyridazine in 80% yield.<sup>20</sup> 4,5-Pyridazinedicarboxylic acid, which is readily obtainable from phthalazine or some properly substituted phthalazines by oxidation,<sup>21</sup> does not readily decarboxylate to pyridazine by usual methods; the best method has been found to be by heating in dilute hydrochloric acid at 200°. <sup>10, 22</sup>

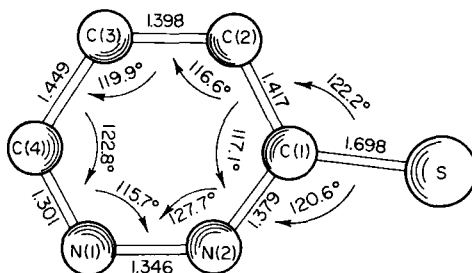


FIG. 1. Dimensions of 3(2H)-pyridazinethione.

Pyridazine can be obtained in reasonable yield from the readily available maleic hydrazide (7) which is converted into 3,6-dichloropyridazine (8) and upon hydrogenolysis of both chlorine atoms pyridazine is formed. Hydrogenolysis over palladium-charcoal catalyst in the presence or absence of sodium hydroxide at atmospheric pressure gives pyridazine in low yield. If the catalytic hydrogenation is performed under pressure and in the presence of ammonia<sup>23</sup> or in aqueous methanolic ammonia solution at ordinary pressure,<sup>24</sup> pyridazine can be obtained in 60 and 67.5% yield, respectively.

The structural dimensions of pyridazine have not been experimentally determined, but spectroscopic investigations, calculations of bond distances and angles,<sup>25-29</sup> and the experimentally determined

<sup>20</sup> A. Wohl and E. Bernreuther, *Ann. Chem.* **481**, 1 (1930).

<sup>21</sup> S. Gabriel, *Chem. Ber.* **36**, 3373 (1903).

<sup>22</sup> R. Stoermer and O. Gaus, *Chem. Ber.* **45**, 3104 (1912).

<sup>23</sup> R. H. Mizsoni and P. E. Spoerri, *J. Am. Chem. Soc.* **73**, 1873 (1951).

<sup>24</sup> T. Itai and H. Igeta, *J. Pharm. Soc. Japan* **74**, 1195 (1954).

<sup>25</sup> S. Carra, S. Polezzo, and M. Simonetta, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **23**, 428 (1957).

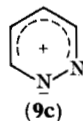
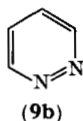
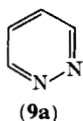
<sup>26</sup> V. J. Berezin, *Opt. i Spektroskopiya* **18**, 136 (1965).

<sup>27</sup> C. A. Coulson, *J. Chem. Soc.*, 5893 (1963).

<sup>28</sup> J. R. de la Vega and H. F. Hametka, *J. Am. Chem. Soc.* **85**, 3504 (1963).

<sup>29</sup> H. Kim and H. F. Hametka, *J. Am. Chem. Soc.* **85**, 1398 (1963).

crystal structure of two pyridazine derivatives—3(2H)-pyridazine-thione<sup>30</sup> (Fig. 1) and 6-oxo-1,6-dihydro-3-pyridazinecarboxamide<sup>31, 32</sup>—revealed that the pyridazine ring is planar and that bond lengths are comparable to those of other azines. They differ significantly from double- or single-bond values, but the N—N bond length is close to the value for a N—N single bond. The nonequivalence of the Kekulé structures **9a** and **9b** for pyridazine has been pointed out<sup>13</sup> and it has been shown that form **9a** contributes more to the structure of pyridazine than does form **9b**. Pyridazine is best considered as a resonance hybrid to which the Kekulé structures **9a** and **9b** and structures with charge distribution such as **9c** contribute.



The resonance energy of pyridazine has been calculated from the experimentally determined heat of combustion to be 12.3 kcal/mole,<sup>33</sup> whereas theoretical calculations relative to the form **9a** gave values of 22,<sup>34</sup> and 36.8 or 39.9 kcal/mole.<sup>35</sup> The latter values are, however, not comparable with experimental resonance energies, as they differ by an unknown amount of compression energy. The conjugation energy was calculated to be 10 kcal/mole.<sup>36</sup> Bond orders<sup>35, 37</sup> and charge densities were calculated for pyridazine<sup>35, 38-43</sup> and its diion<sup>38</sup>

<sup>30</sup> C. H. Carlisle and M. B. Hossain, *Acta Cryst.* **21**, 249 (1966).

<sup>31</sup> P. Cucka and R. W. H. Small, *Acta Cryst.* **7**, 199 (1954).

<sup>32</sup> P. Cucka, *Acta Cryst.* **16**, 318 (1963).

<sup>33</sup> J. Tjebbes, *Acta Chem. Scand.* **16**, 916 (1962).

<sup>34</sup> A. Maccoll, *J. Chem. Soc.*, 670 (1946).

<sup>35</sup> D. W. Davies, *Trans. Faraday Soc.* **51**, 449 (1955).

<sup>36</sup> J. D. Cox, *Tetrahedron* **19**, 1175 (1963).

<sup>37</sup> A. Lofthus, *Mol. Phys.* **2**, 367 (1959).

<sup>38</sup> K. Jankowski, *Bull. Acad. Polon. Sci., Ser. Sci., Math., Astron. Phys.* **11**, 621 (1963).

<sup>39</sup> O. Chalvet and S. Sandorfy, *Compt. Rend.* **228**, 566 (1949).

<sup>40</sup> R. McWeeny and T. E. Peacock, *Proc. Phys. Soc. (London)* **A70**, 41 (1957).

<sup>41</sup> S. Basu, *Proc. Natl. Inst. India* **A21**, 173 (1955).

<sup>42</sup> T. E. Peacock, *J. Chem. Soc.*, 1946 (1960).

<sup>43</sup> M. Iwaizumi, *Nippon Kagaku Zasshi* **82**, 306 (1961).

using different methods. The ionization potential of pyridazine, which is largely determined by the nonbonding electrons of the nitrogen atom, has been calculated and experimentally measured.<sup>40, 44, 45</sup> Correlation of the experimental value with those of other diazines and pyridine (Table I) reveals parallelism between the ease of ionization and the basicity of azines.<sup>44</sup> Likewise, the calculated (3.6 to 4.0 D<sup>25, 35, 46-51</sup>) and experimentally observed (3.94 D<sup>47, 50</sup>) values for the dipole moment of pyridazine are in good agreement. These figures agree with the hypothesis that two neighboring nitrogen atoms in pyridazine have greater electron-acceptor properties than one nitrogen atom (pyrimidine).

In the series of six-membered heterocycles pyridazine has a high boiling point (208°/760 mm,<sup>10</sup> 207.4°/762.5 mm<sup>53</sup>) which suggested association. A reinvestigation of intermolecular association in liquid pyridazine, in which evidence for the existence of a discrete dimer has been adduced,<sup>53</sup> has shown<sup>54</sup> that such a dimer does not exist. The intermolecular attraction can therefore be attributed to electrostatic forces arising from the high permanent dipole.

Among diazines, pyridazine has a relatively high  $pK_a$  value (Table I). In general, the introduction of a second nitrogen in the pyridine ring diminishes considerably the basicity and this decrease is in accordance with the theoretical calculations of free valence indices<sup>39</sup> of the nitrogen atoms. The relatively high  $pK_a$  of pyridazine has been attributed<sup>52</sup> to resonance stabilization of the pyridazinium ion.

<sup>44</sup> T. Nakajima and A. Pullman, *Compt. Rend.* **246**, 1047 (1958).

<sup>45</sup> I. Omura, H. Baba, K. Higasi, and Y. Kanaoka, *Bull. Chem. Soc. Japan* **30**, 633 (1957).

<sup>46</sup> A. T. Amos and G. G. Hall, *Mol. Phys.* **4**, 25 (1961).

<sup>47</sup> I. Mazeika, L. Avota, G. Sokolov, and S. Hillers, *Tr. Soveshch. po Fiz. Metodam Issled. Organ. Soedin. i Khim. Protessov, Akad. Nauk Kirg. SSR, Inst. Organ. Khim., Frunze, 1962*, p. 68 (1964); *Chem. Abstr.* **62**, 3495 (1965).

<sup>48</sup> I. Mazeika, L. Avota, G. Sokolov, and S. Giller, *Zh. Obshch. Khim.* **34**, 3380 (1964).

<sup>49</sup> L. E. Orgel, T. L. Cottrell, W. Dick, and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).

<sup>50</sup> W. C. Schneider, *J. Am. Chem. Soc.* **70**, 627 (1948).

<sup>51</sup> P. O. Löwdin, *J. Chem. Phys.* **19**, 1323 (1951).

<sup>52</sup> A. Albert, R. J. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

<sup>53</sup> W. Hückel and W. Jahnentz, *Chem. Ber.* **75B**, 1438 (1942).

<sup>54</sup> P. Coad, R. A. Coad, and C. L. Wilkins, *J. Phys. Chem.* **67**, 2815 (1963).

<sup>55</sup> H. F. Hameka and A. M. Liquori, *Mol. Phys.* **1**, 9 (1958).

<sup>56</sup> J. Levisalles, *Bull. Soc. Chim. France*, 1009 (1957).

Several spectroscopic investigations concerning pyridazine have been performed. Pyridazine is isoelectronic with benzene and replacement of CH groups in the latter by the more electronegative nitrogen atoms causes a marked difference, alike with the other two diazines, in the near ultraviolet spectrum. It has a highly aromatic type of absorption spectrum. The ultraviolet spectra of pyridazine, its anion, and cation have been measured in different solvents, calculated, and interpreted.<sup>13, 23, 34, 38, 54, 57-73</sup> A detailed discussion

TABLE I

Compound	pK <sub>H</sub> <sup>+</sup> <sup>a</sup>	Ionization potential (exp) (ev)	Dipole moment (exp) (D) <sup>b</sup>	Free valence index
Pyridine	5.23	9.76	2.15	1.211
Pyridazine	2.33, 2.98 <sup>c</sup>	9.86	3.94	1.153
Pyrimidine	1.30	9.91	2.10	1.196
Pyrazine	0.6	10.01	—	1.154

<sup>a</sup> pK values are taken from A. Albert, R. J. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

<sup>b</sup> Values for pyridine and pyrimidine are taken from H. F. Hamerka and A. M. Liquori, *Mol. Phys.* **1**, 9 (1958).

<sup>c</sup> J. Levisalles, *Bull. Soc. Chim. France*, 1009 (1957).

<sup>57</sup> F. Halverson and R. C. Hirt, *J. Chem. Phys.* **17**, 1165 (1949).

<sup>58</sup> L. Goodman, *J. Mol. Spectry.* **6**, 109 (1961).

<sup>59</sup> D. R. Kearns, *J. Chem. Phys.* **38**, 1508 (1963).

<sup>60</sup> J. N. Murell, *Mol. Phys.* **1**, 384 (1958).

<sup>61</sup> G. Favini, I. Vandoni, and M. Simonetta, *Theoret. Chim. Acta* **3**, 45 (1965).

<sup>62</sup> K. K. Innes, J. A. Merrit, W. C. Tincher, and S. G. Tilford, *Nature* **187**, 500 (1960).

<sup>63</sup> J. E. Parkin and K. K. Innes, *J. Mol. Spectry.* **15**, 407 (1965).

<sup>64</sup> L. Goodman and R. W. Harrel, *J. Chem. Phys.* **30**, 1131 (1959).

<sup>65</sup> M. A. El Sayed and G. W. Robinson, *J. Chem. Phys.* **34**, 1840 (1961).

<sup>66</sup> S. Carra, E. Gianinetti, and M. Simonetta, *Atti. Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat.* [8] **24**, 722 (1958).

<sup>67</sup> G. J. Brealey and M. Kasha, *J. Am. Chem. Soc.* **77**, 4462 (1955).

<sup>68</sup> M. Iwaizumi and H. Azumi, *Nippon Kagaku Zasshi* **84**, 694 (1963).

<sup>69</sup> J. W. Dodd, F. J. Hopton, and N. S. Hush, *Proc. Chem. Soc.*, 61 (1962).

<sup>70</sup> K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta* **37**, 1298 (1954).

<sup>71</sup> R. H. Linnell, F. Raab, and R. Clifford, *J. Phys. Chem.* **68**, 1999 (1964).

<sup>72</sup> A. K. Chandra and S. Basu, *Trans. Faraday Soc.* **56**, 632 (1960).

<sup>73</sup> G. Favini and M. Simonetta, *Atti Accad. Nazl. Lincei, Rend., Classe. Sci. Fis., Mat. Nat.* [8] **28**, 57 (1960).



is presented by Mason.<sup>74</sup> The lower-energy diazine band near 3333 Å is assigned to a nitrogen nonbonding electron transition ( $n \rightarrow \pi^*$ ) and the high-energy band near 2500 Å to a  $\pi$  electron ( $\pi \rightarrow \pi^*$ ) transition.<sup>75, 76</sup> The observed red shift does not agree well with the calculated value and this is interpreted in terms of an inequality of the energy of the lone pair orbitals in pyridazine as a result of their strong mutual interaction.<sup>74</sup> The blue shift of pyridazine on changing from hexane to more polar solvents has been shown to be due mainly to the hydrogen bonding of a hydroxylic solvent to a nitrogen lone pair of electrons. For example, with increase of ethanol concentration the amount of the hydrogen-bonded species increases and at any given concentration of ethanol in hexane the bonded and nonbonded species are in equilibrium.<sup>67</sup> From the UV data the association constant of hydrogen bonding has been obtained (4.2 kcal) and this is close to the value (4.6 kcal) found from a study of association by infrared techniques.<sup>67</sup> The relatively large solvent shift of pyridazine on changing from hydrocarbon to water has been ascribed to the double hydrogen bonding (about 10 kcal) between one molecule of water and both pyridazine ring nitrogens.<sup>77</sup>

Complete infrared and Raman data for pyridazine are given<sup>78</sup> and assignments were made. A review by Katritzky and Ambler<sup>79</sup> includes infrared data for pyridazine and other heteroaromatic compounds. Infrared spectroscopy has been applied also to the study of hydrogen-bonded complexes with phenol.<sup>80</sup> Calculations on the vibrational spectrum of pyridazine have been performed.<sup>26</sup>

Similarly, NMR studies on pyridazine have been carried out.<sup>54, 81-87</sup>

<sup>74</sup> S. F. Mason, *J. Chem. Soc.*, 1240 (1959).

<sup>75</sup> F. Halverson and R. C. Hirt, *J. Chem. Phys.* **19**, 711 (1951).

<sup>76</sup> R. H. Horning and E. D. Amstutz, *J. Org. Chem.* **20**, 1069 (1955).

<sup>77</sup> R. H. Linnell, *J. Chem. Phys.* **34**, 698 (1961).

<sup>78</sup> R. C. Lord, A. L. Marston, and F. A. Miller, *Spectrochim. Acta* **9**, 113 (1957).

<sup>79</sup> A. R. Katritzky and A. P. Ambler, *Phys. Methods Heterocyclic Chem.* **2**, 161 (1963).

<sup>80</sup> H. Fritzsche and H. Dunker, *Acta Chim. Acad. Sci. Hung.* **40**, 37 (1964).

<sup>81</sup> N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog." Varian Assoc., Palo Alto, California, 1963.

<sup>82</sup> J. A. Elvidge, G. T. Newbold, I. R. Sencially, and T. G. Symes, *J. Chem. Soc.*, 4157 (1964).

<sup>83</sup> T. Declercq, R. Degroote, J. de Lannoy, R. Nasielski-Hinkens, and J. Nasielski, *Bull. Soc. Chim. Belges* **74**, 119 (1965).

The NMR spectrum of pyridazine shows two symmetrical quartets of  $A_2X_2$  type and  $\tau$  values and coupling constants are as follows:  $\tau_3 = \tau_6 = 0.76$ ,  $\tau_4 = \tau_5 = 2.45$ ;  $J_{3,4} = J_{5,6} = 4.9$  ( $5.05^{84}$ ),  $J_{3,5} = J_{4,6} = 2.0$ ,  $J_{3,6} = 3.5$  ( $1.4^{84}$ ),  $J_{4,5} = 8.4$ .<sup>86</sup> The  $^{13}\text{C}$  satellites in natural abundance in the liquid state have been examined in order to obtain a complete set of proton magnetic resonance parameters for pyridazine.<sup>84, 86</sup> It has been found that chemical shifts are strongly concentration-dependent in a sense opposite to that normally found with aromatic compounds. Coupling constants are, however, virtually invariant. From the NMR spectrum, a deshielding effect on the hydrogen atoms at positions 3 and 6 is revealed.<sup>54</sup>

Examinations of other physical properties of pyridazine include the ESR spectrum of pyridazine radical anion (obtained with pyridazine and sodium or potassium in dimethoxyethane or tetrahydrofuran,<sup>88-90</sup> the self-diffusion coefficient and activation energy,<sup>91</sup> the half-wave potential ( $-2.16\text{V}$ ),<sup>89</sup> and magnetic susceptibility.<sup>92</sup> Pyridazine was reported not to fluoresce<sup>93</sup> and no luminiscence could be observed even under very long exposures.<sup>94</sup> More recently, room-temperature fluorescence in solution is reported to be at  $23,800\text{ cm}^{-1}$  (max.), with a life time of  $2.6 \times 10^{-9}$ .<sup>95</sup>

Although pyridazine is related to pyrimidine, its chemical reactivity differs in many respects as a result of the very polar nature of the molecule. Chemically, pyridazine is expected to undergo nucleophilic substitution as a consequence of the positive nature of the ring carbons, and to resist electrophilic attack. This has been confirmed in studies of many substituted pyridazines. Pyridazine forms salts

<sup>84</sup> V. M. S. Gil, *Mol. Phys.* **9**, 443 (1965).

<sup>85</sup> J. A. Elvidge and P. D. Ralph, *J. Chem. Soc. B, Phys. Org.*, 249 (1966).

<sup>86</sup> K. Tori and M. Ogata, *Chem. Pharm. Bull. (Tokyo)* **12**, 272 (1964).

<sup>87</sup> J. N. Murell and V. M. S. Gil, *Trans. Faraday Soc.* **61**, 402 (1965).

<sup>88</sup> C. A. McDowell, K. F. Paulus, and J. R. Rowlands, *Proc. Chem. Soc.*, 60 (1962).

<sup>89</sup> E. W. Stone and A. H. Maki, *J. Chem. Phys.* **39**, 1635 (1963).

<sup>90</sup> R. L. Ward, *J. Am. Chem. Soc.* **84**, 332 (1962).

<sup>91</sup> D. W. McCall, D. C. Douglass, and E. W. Anderson, *Ber. Bunsenges. Phys. Chem.* **67**, 336 (1963).

<sup>92</sup> H. Francois, *Bull. Soc. Chim. France*, 515 (1962).

<sup>93</sup> M. A. El Sayed, *J. Chem. Phys.* **36**, 573 (1962).

<sup>94</sup> L. Goodman and V. G. Krishna, *Rev. Mod. Phys.* **35**, 541 (1963).

<sup>95</sup> B. J. Cohen, H. Baba, L. Goodman, *J. Chem. Phys.* **43**, 2902 (1965).

with strong acids, metal complexes were obtained,<sup>96-98</sup> and charge-transfer complexes with tetracyanoethylene were investigated.<sup>99</sup> Deuteration of pyridazine revealed that hydrogen atoms at positions 4 and 5 are more easily deuterated in alkaline medium than those at positions 3 and 6.<sup>100, 101</sup>

With sodium in ethanol pyridazine is reduced to hexahydropyridazine; 1,4-diaminobutane is also obtained.<sup>14</sup> It can form quaternary salts, but no bisquaternization was found.<sup>102</sup> A survey of the quarternization of pyridazines and other heterocycles is given in Volume 3, Chapter 1 of this Series. For alkylation and arylation of pyridazine see Section IV of the present chapter.

Pyridazine reacts with dimethylacetylenedicarboxylate in methanol to give only trimethylpyrrolo[1,2-*b*]pyridazine-5,6,7-tricarboxylate, but in acetonitrile tetramethyl-8*H*-pyrido[1,2-*b*]pyridazine-5,6,7,8-tetracarboxylate was also obtained, as the main product.<sup>18, 103</sup> Analogously, pyridazine adds 2 molecules of maleic anhydride to form a 1 : 2 adduct.<sup>104</sup>

### III. General Synthetic Methods

There are two basic principles for obtaining pyridazines. The ring may be built up directly from aliphatic components, one of these being usually an unsubstituted or substituted hydrazine. Another and less common approach makes use of different heterocyclic systems as starting materials.

This Section includes only synthetic methods for the ring; other transformations are dealt with later.

<sup>96</sup> C. Reimann and G. Gordon, *Nature* **205**, 902 (1965).

<sup>97</sup> G. Spacu, P. Spacu, and E. Radulescu, *Analele Univ. "C. I. Parhon" Bucuresti, Ser. Stiint. Nat.* **13**, 64 (1957).

<sup>98</sup> E. E. Aynsley and W. A. Campbell, *J. Chem. Soc.*, 832 (1957).

<sup>99</sup> C. Nicolau and C. Cailly, *Bull. Classe Sci., Acad. Roy. Belg.* [5] **51**, 181 (1965).

<sup>100</sup> G. E. Calf and J. L. Garnett, *J. Catalysis* **3**, 461 (1964).

<sup>101</sup> Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull. (Tokyo)* **12**, 138 (1964).

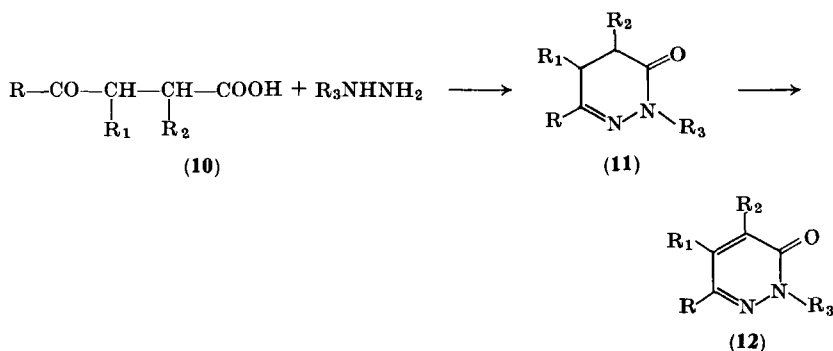
<sup>102</sup> A. E. Blood and C. R. Noller, *J. Org. Chem.* **22**, 844 (1957).

<sup>103</sup> R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C. Org.*, 2218 (1966).

<sup>104</sup> R. C. Cookson and N. S. Isaacs, *Tetrahedron* **19**, 1237 (1963).

## A. FROM 1,4-KETOACIDS

The formation of pyridazines from 1,4-ketoacids (**10**) or their esters and unsubstituted or substituted hydrazines is one of the most widely used methods of synthesis. It is possible to conduct the reaction in a single step or via the intermediate hydrazones or semicarbazones. The resulting 4,5-dihydro-3(2*H*)-pyridazinones (**11**) are then converted into the corresponding 3(2*H*)-pyridazinones (**12**) upon dehydrogenation. Bromine in glacial acetic acid is the commonest and most useful



oxidizing agent to bring about this transformation, although a variety of other reagents have been used. It has been found that the success of dehydrogenation is greatly influenced by the position and number of substituents in the pyridazine ring.<sup>105</sup> A uniform product has been obtained also when a mixture of isomeric partially hydrogenated pyridazines was oxidized.<sup>106</sup>

A variety of 1,4-ketoacids have been used as starting material. In these (**10**),  $\text{R}_1$  or  $\text{R}_2$  is usually hydrogen (but also alkyl or aryl groups),

<sup>105</sup> E. Jucker and R. Süess, *Helv. Chim. Acta* **42**, 2506 (1959).

<sup>106</sup> E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.* **75**, 1117 (1953).

<sup>107</sup> F. Ach, *Ann. Chem.* **253**, 44 (1889).

<sup>108</sup> M. Asamo and T. Azumi, *Chem. Ber.* **68B**, 991 (1935).

<sup>109</sup> N. Beaugeard and J. Matti, *Bull. Soc. Chim. France*, 1612 (1956).

<sup>110</sup> P. Brown, J. Burdon, T. T. Smith, and J. C. Tatlow, *Tetrahedron* **10**, 164 (1960).

<sup>111</sup> B. Camerino and B. Patelli, *Farmaco (Pavia), Ed. Sci.* **11**, 446 (1956).

<sup>112</sup> T. Curtius, *J. Prakt. Chem.* **50**, 508 (1894).

<sup>113</sup> T. Curtius, *J. Prakt. Chem.* [2] **85**, 137 (1912).

whereas R can be an alkyl or aralkyl group,<sup>105, 107-130</sup> a carboxy or carbethoxy group,<sup>12, 13, 131-137</sup> an aromatic,<sup>11, 105, 106, 138-171</sup> heterocyclic,<sup>172-177</sup> or even ferrocenyl<sup>178</sup> residue. Less frequently 1,4-aldehydoacids were employed, readily forming **11** (R = H).<sup>179-182</sup>

Several pyridazines were prepared unintentionally by the attempted Wolff-Kishner reduction of ketoacids. It has been claimed<sup>183</sup> that the ease of pyridazine formation during the Wolff-Kishner-Huang-Minlon reduction of aromatic 1,4-ketoacids depends on the nature of

- <sup>114</sup> T. Curtius, *J. Prakt. Chem.* [2] **85**, 393 (1912).  
<sup>115</sup> C. Grundmann, *Chem. Ber.* **81**, 1 (1948).  
<sup>116</sup> J. Levisalles, *Bull. Soc. Chim. France*, 1004 (1957).  
<sup>117</sup> W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 239 (1947).  
<sup>118</sup> A. A. Ponomarev and V. A. Sedavkina, *Zh. Obshch. Khim.* **32**, 2540 (1962).  
<sup>119</sup> N. A. Preobrashenski, M. N. Sechtschukina, and A. F. Wompe, *Chem. Ber.* **69B**, 1618 (1936).  
<sup>120</sup> A. Steecke, *Ann. Chem.* **242**, 367 (1887).  
<sup>121</sup> R. Stoermer and H. Stroh, *Chem. Ber.* **68B**, 2112 (1935).  
<sup>122</sup> S. Veibel, *Acta Chem. Scand.* **1**, 54 (1947).  
<sup>123</sup> L. Wolff, *Ann. Chem.* **394**, 86 (1912).  
<sup>124</sup> H. Gault and T. Salomon, *Compt. Rend.* **175**, 274 (1922).  
<sup>125</sup> H. Gault and T. Salomon, *Ann. Chim. (Paris)* [10] **2**, 133 (1924).  
<sup>126</sup> R. H. Horning and E. D. Amstutz, *J. Org. Chem.* **20**, 707 (1955).  
<sup>127</sup> K. Mitsuhashi and S. Shiotani, *Yakugaku Zasshi* **80**, 1348 (1960); *Chem. Abstr.* **55**, 5519 (1961).  
<sup>128</sup> C. M. Atkinson and R. E. Rodway, *J. Chem. Soc.*, 6 (1959).  
<sup>129</sup> A. Maeder, *Helv. Chim. Acta* **29**, 120 (1946).  
<sup>130</sup> J. G. Michels, G. C. Wright, and G. Gever, *J. Med. Chem.* **9**, 612 (1966).  
<sup>131</sup> E. E. Blaise and H. Gault, *Bull. Soc. Chim. France* **9**, 451 (1911).  
<sup>132</sup> H. Gault, G. Kalopissis, N. Rist, and F. Grumbach, *Bull. Soc. Chim. France*, 916 (1954).  
<sup>133</sup> A. W. K. de Jong, *Ann. Chem.* **319**, 121 (1901).  
<sup>134</sup> G. B. Kline and S. H. Cox, *J. Org. Chem.* **26**, 1854 (1961).  
<sup>135</sup> R. Rothenburg, *Chem. Ber.* **26**, 2061 (1893).  
<sup>136</sup> S. Sakurai and Y. Komachiya, *Nippon Kagaku Zasshi* **82**, 490 (1961).  
<sup>137</sup> W. Wislicenus and M. Waldmüller, *Chem. Ber.* **44**, 1564 (1911).  
<sup>138</sup> T. Abdel-Nour, F. G. Baddar, and A. K. Fateen, *J. Chem. Soc.*, 5302 (1964).  
<sup>139</sup> G. K. Almström, *Ann. Chem.* **400**, 131 (1913).  
<sup>140</sup> F. G. Baddar, N. Latif, and A. A. Nada, *J. Chem. Soc.*, 7005 (1965).  
<sup>141</sup> W. Borsche and H. Schmidt, *Chem. Ber.* **72B**, 1827 (1939).  
<sup>142</sup> E. Buchta and H. Schamberger, *Chem. Ber.* **92**, 1363 (1959).  
<sup>143</sup> W. Borsche and H. Sauerheimer, *Chem. Ber.* **47**, 1645 (1914).  
<sup>144</sup> W. Borsche, P. Hofmann, and H. Kühn, *Ann. Chem.* **554**, 23 (1943).

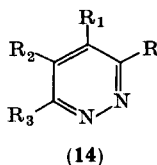
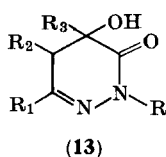
the aryl group, the reaction being competitive with the normal reduction. The formation of pyridazinones is suppressed if esters are used instead of acids. In a somewhat lengthy procedure hydrazones are prepared first and the cyclization step is performed separately. This can be done with hot acetic acid or anhydride, polyphosphoric acid, or dilute mineral acids,<sup>129, 184-188</sup> or merely by heating.<sup>137, 183, 189-194</sup> Hydrazones of 1,4-aldehydroacids cyclize similarly<sup>179, 195-198</sup> and some pyridazinones are formed easily at room temperature.

- <sup>145</sup> O. Brunner and P. Hanke, *Monatsh. Chem.* **85**, 88 (1954).  
<sup>146</sup> E. Buchta and F. Güllich, *Chem. Ber.* **92**, 916 (1959).  
<sup>147</sup> G. R. Clemo and H. G. Dickenson, *J. Chem. Soc.*, 255 (1937).  
<sup>148</sup> J. F. Eijkman, *Chem. Weekblad* **1**, 349 (1904).  
<sup>149</sup> J. Drucey and B. H. Ringier, *Helv. Chim. Acta* **34**, 195 (1951).  
<sup>150</sup> S. Biniecki, A. Haase, J. Izdebski, E. Kesler, and L. Rylski, *Bull. Acad. Polon. Sci., Ser. Sci., Chim., Geol. Geograph.* **6**, 237 (1958).  
<sup>151</sup> R. Fittig, *Ann. Chem.* **299**, 1 (1898).  
<sup>152</sup> A. C. O. Hann and A. Lapworth, *J. Chem. Soc.* **85**, 1355 (1904).  
<sup>153</sup> R. D. Haworth, B. P. Moore, and P. L. Pauson, *J. Chem. Soc.*, 3271 (1949).  
<sup>154</sup> A. Katzenellenbogen, *Chem. Ber.* **34**, 3828 (1901).  
<sup>155</sup> M. Kugel, *Ann. Chem.* **299**, 50 (1898).  
<sup>156</sup> D. Libermann and A. Rouaix, *Bull. Soc. Chim. France*, 1793 (1959).  
<sup>157</sup> H. Limpricht, *Ann. Chem.* **312**, 110 (1900).  
<sup>158</sup> F. Mayer and W. Krieger, *Chem. Ber.* **55B**, 1659 (1922).  
<sup>159</sup> Y. Nitta, F. Yoneda, T. Ohtaka, and T. Kato, *Chem. Pharm. Bull. (Tokyo)* **12**, 69 (1964).  
<sup>160</sup> A. Oppenheim, *Chem. Ber.* **34**, 4227 (1901).  
<sup>161</sup> O. Poppenberg, *Chem. Ber.* **34**, 3257 (1901).  
<sup>162</sup> S. Skraup and E. Schwamberger, *Ann. Chem.* **462**, 135 (1928).  
<sup>163</sup> L. I. Smith and Chien-Pen Lo, *J. Am. Chem. Soc.* **70**, 2209 (1948).  
<sup>164</sup> I. Zugravescu, M. Petrovanu, and E. Rucinski, *Rev. Chim., Acad. Rep. Populaire Roumaine* **7**, 1405 (1962).  
<sup>165</sup> R. Pummerer and E. Buchta, *Chem. Ber.* **69**, 1005 (1936).  
<sup>166</sup> R. Schmiechen and H. Gibian, *Ann. Chem.* **665**, 68 (1963).  
<sup>167</sup> H. M. Taylor and C. R. Hauser, *J. Am. Chem. Soc.* **82**, 1790 (1960).  
<sup>168</sup> P. Yates and D. G. Farnum, *J. Am. Chem. Soc.* **85**, 2967 (1963).  
<sup>169</sup> I. Crossland and L. K. Rasmussen, *Acta Chem. Scand.* **19**, 1652 (1965).  
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<sup>171</sup> R. Royer, E. Bisagni, and G. Menichi, *Bull. Soc. Chim. France*, 2112 (1964).  
<sup>172</sup> J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, K. Clarke, S. Eardley, B. E. Jennings, and A. Robertson, *J. Chem. Soc.*, 2222 (1957).  
<sup>173</sup> H. A. Burch and L. E. Benjamin, *J. Med. Chem.* **9**, 425 (1966).  
<sup>174</sup> O. G. Holland and E. D. Amstutz, *Rec. Trav. Chim.* **83**, 1047 (1964).

Several pyridazinones were obtained directly from **10** or its ester and semicarbazide<sup>199</sup> or a thiohydrazide<sup>200</sup> or from pyrolytic decomposition of semicarbazones to **12** ( $R_3 = H$ ).<sup>117, 192, 201, 202</sup> Semicarbazones of these esters were also successfully cyclized to **11** ( $R_3 = H$ ) in the presence of ethanolic ammonia,<sup>203</sup> but heating or reductive cyclization ( $Pd/H_2$  or  $Na/Hg$ ) yielded the reduced pyridazinones with a carboxamido group attached to the ring nitrogen.<sup>204-206</sup>

- <sup>175</sup> E. B. Knott, *J. Chem. Soc.*, 1190 (1947).  
<sup>176</sup> A. N. Kost, V. N. Eraksina, and E. V. Vinogradova, *Zh. Organ. Khim.* **1**, 129 (1965).  
<sup>177</sup> R. Royer, M. Hubert-Habart, L. Rene, and A. Cheutin, *Bull. Soc. Chim. France*, 1259 (1964).  
<sup>178</sup> J. Tirouflet, B. Gautheron, and R. Dabard, *Bull. Soc. Chim. France*, 96 (1965).  
<sup>179</sup> M. Amorosa and L. Lipparini, *Ann. Chim. (Rome)* **49**, 322 (1959).  
<sup>180</sup> E. E. Blaise, *Compt. Rend.* **153**, 71 (1911).  
<sup>181</sup> E. Carriere, *Ann. Chim. (Rome)* **17**, 38 (1921).  
<sup>182</sup> E. Sugawara and K. Kohno, *Pharm. Bull. (Tokyo)* **4**, 477 (1956).  
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<sup>184</sup> N. H. Cromwell, K. E. Cook, and P. L. Creger, *J. Am. Chem. Soc.* **78**, 4416 (1956).  
<sup>185</sup> L. De Bellis and M. L. Stein, *Ann. Chim. (Rome)* **51**, 663 (1961).  
<sup>186</sup> V. V. Feofilaktov and N. K. Semenova, *Zh. Obshch. Khim.* **23**, 849 (1953).  
<sup>187</sup> I. Satoda, T. Fukui, and K. Mori, *Yakugaku Zasshi* **82**, 302 (1962).  
<sup>188</sup> W. Davey and D. J. Tivey, *J. Chem. Soc.*, 1230 (1958).  
<sup>189</sup> L. Mungioni, *Gazz. Chim. Ital.* **45**, 299 (1915).  
<sup>190</sup> F. J. Stevens, T. D. Griffin, and T. L. Fields, *J. Am. Chem. Soc.* **77**, 42 (1955).  
<sup>191</sup> T. Takubo, T. Tadaoka, and T. Sawai, *Yakugaku Zasshi* **79**, 830 (1959).  
<sup>192</sup> V. F. Kucherov, *Zh. Obshch. Khim.* **20**, 1662 (1950).  
<sup>193</sup> W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 549 (1947).  
<sup>194</sup> H. Gregory and L. F. Wiggins, *J. Chem. Soc.*, 2546 (1949).  
<sup>195</sup> M. Amorosa and A. Guarnieri, *Gazz. Chim. Ital.* **90**, 1056 (1960).  
<sup>196</sup> J. Schreiber and C. G. Wermuth, *Compt. Rend.* **250**, 2587 (1960).  
<sup>197</sup> F. J. Stevens and S. W. Fox, *J. Am. Chem. Soc.* **70**, 2263 (1948).  
<sup>198</sup> N. N. Suvorov and V. S. Murasheva, *Zh. Obshch. Khim.* **30**, 3112 (1960).  
<sup>199</sup> S. C. De and D. N. Dutt, *J. Indian Chem. Soc.* **7**, 473 (1930).  
<sup>200</sup> B. Holmberg, *Arkiv Kemi, Mineral. Geol.* **25A**, No. 18 (1947).  
<sup>201</sup> H. Pechmann, *Chem. Ber.* **33**, 3323 (1900).  
<sup>202</sup> J. Thiele and H. Rössner, *Ann. Chem.* **306**, 201 (1899).  
<sup>203</sup> J. Thiele, *Ann. Chem.* **306**, 145 (1899).  
<sup>204</sup> P. Ruggli and A. Maeder, *Helv. Chim. Acta* **25**, 936 (1942).

Less frequently, unsaturated 1,4-ketoacids were employed and these<sup>11, 207-209</sup> or their hydrazones<sup>184, 193</sup> afford **12** directly. Synthesis of **12** is also possible from unsaturated  $\gamma$ -lactones<sup>138, 165, 210-213</sup> and 3-bromo-,<sup>214</sup> 3-alkylthio-,<sup>215</sup> or 2-hydroxy-1,4-ketoacids.<sup>133, 216</sup> The reaction takes place with simultaneous elimination of water or other residues, although it is claimed that in some cases the elimination of water is slower since the corresponding 4-hydroxy derivatives (**13**) were isolated.<sup>217, 218</sup> However, the structure of the latter compounds



has not been proved. A particular case is the reaction of  $\alpha$ -hydroxy-levulinic aldehyde, an intermediate in the Webb color reaction for 2-deoxyaldoses, with arylhydrazines to give 1-arylpuridinium salts in acid solution.<sup>219</sup>

- <sup>205</sup> J. Bougault, E. Cattelain, and P. Chabrier, *Compt. Rend.* **225**, 876 (1947).  
<sup>206</sup> H. Machemer, *Chem. Ber.* **66B**, 1031 (1933).  
<sup>207</sup> T. Ajello and S. Cusmano, *Gazz. Chim. Ital.* **70**, 765 (1940).  
<sup>208</sup> J. H. Birkinshaw, A. E. Oxford, and H. Raistrick, *Biochem. J.* **30**, 394 (1936).  
<sup>209</sup> S. Dixon, H. Gregory, and L. F. Wiggins, *J. Chem. Soc.*, 2139 (1949).  
<sup>210</sup> J. A. Giles and J. N. Schumacher, *Tetrahedron* **14**, 246 (1961).  
<sup>211</sup> A. Mustafa, S. A. Khattab, and W. Asker, *Can. J. Chem.* **41**, 1813 (1963).  
<sup>212</sup> Y. Iwakura, K. Nagakubo, and K. Hayashi, *Nippon Kagaku Zasshi* **78**, 746 (1957); *Chem. Abstr.* **54**, 5449 (1960).  
<sup>213</sup> Y. Iwakura, N. Nagakubo, and K. Hayashi, *Kogyo Kagaku Zasshi* **59**, 476 (1956); *Chem. Abstr.* **52**, 3759 (1958).  
<sup>214</sup> I. Kumashiro, *Nippon Kagaku Zasshi* **82**, 928 (1961); *Chem. Abstr.* **57**, 11183 (1962).  
<sup>215</sup> G. Claeson, *Arkiv Kemi* **11**, 285 (1957).  
<sup>216</sup> J. Levisalles and P. Baranger, *Compt. Rend.* **242**, 1336 (1956).  
<sup>217</sup> C. Arnengaud, C. G. Wermuth, and J. Schreiber, *Compt. Rend.* **254**, 2181 (1962).  
<sup>218</sup> M. Chaker and J. Schreiber, *Compt. Rend.* **246**, 3646 (1958).  
<sup>219</sup> K. Himmelsbach and O. Westphal, *Ann. Chem.* **668**, 165 (1963).



## B. FROM 1,4-DIKETONES

Many alkyl- or aryl-substituted pyridazines (**14**) have been prepared by a direct one-step cyclization from an unsaturated 1,4-diketone (diacylethylene) and hydrazine. In the main symmetrically substituted diketones were employed, carrying aliphatic<sup>220</sup> or aromatic<sup>221-229</sup> groups. Ethylene-substituted unsaturated 1,4-diketones afford tri- or tetrasubstituted pyridazines (**14**,  $R = R_1 = R_2 = R_3 = \text{alkyl or aryl}$ ).<sup>230-236</sup>

Cis isomers are preferentially used. Trans isomers are reported to be less reactive<sup>228</sup> or failed to give pyridazines.<sup>227</sup> However, some hydrazones of trans isomers, upon heating in glacial acetic acid, form **14** and the reaction involves slow isomerization as indicated with dibenzoylethylene.<sup>222</sup> Here, the cis isomer forms immediately (**14**,  $R_1 = R_2 = H$ ,  $R = R_3 = Ph$ ) in almost quantitative yield at room temperature, whereas the trans isomer upon heating with hydrazine in acetic acid gives the same product in low yield. Instead of hydrazine, semicarbazide, thiosemicarbazide and aminoguanidine have also been used to build up the pyridazine ring.<sup>221</sup>

From saturated 1,4-diketones two types of dihydropyridazines can be prepared. 4,5-Dihydropyridazines (**15**) are formed in the reaction

<sup>220</sup> J. Levisalles and P. Baranger, *Compt. Rend.* **240**, 444 (1955).

<sup>221</sup> H. Beyer, T. Pyl, and C. E. Völcker, *Ann. Chem.* **638**, 150 (1960).

<sup>222</sup> N. Campbell and N. M. Khanna, *J. Chem. Soc. Suppl. No. 1*, 33 (1949).

<sup>223</sup> G. Dupont and J. Germain, *Compt. Rend.* **223**, 743 (1946).

<sup>224</sup> J. L. E. Erickson, J. M. Dechary, and M. R. Kesling, *J. Am. Chem. Soc.* **73**, 5301 (1951).

<sup>225</sup> T. Ajello, V. Sprio, and P. Madonia, *Gazz. Chim. Ital.* **87**, 11 (1957).

<sup>226</sup> H. Keller, R. Pasternak, and H. von Halban, *Helv. Chim. Acta* **29**, 512 (1946).

<sup>227</sup> R. E. Lutz and S. M. King, *J. Org. Chem.* **17**, 1519 (1952).

<sup>228</sup> C. Paal and H. Schulze, *Chem. Ber.* **33**, 3784 (1900).

<sup>229</sup> C. Paal and H. Schulze, *Chem. Ber.* **33**, 3795 (1900).

<sup>230</sup> V. Sprio and P. Madonia, *Gazz. Chim. Ital.* **85**, 965 (1955).

<sup>231</sup> V. Sprio and P. Madonia, *Gazz. Chim. Ital.* **86**, 101 (1956).

<sup>232</sup> R. F. Japp and J. Wood, *J. Chem. Soc.* **87**, 707 (1905).

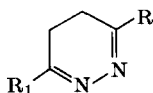
<sup>233</sup> P. Yates, D. G. Farnum, and G. H. Stout, *J. Am. Chem. Soc.* **80**, 196 (1958).

<sup>234</sup> P. Yates, D. G. Farnum, and G. H. Stout, *Chem. & Ind. (London)*, 821 (1956).

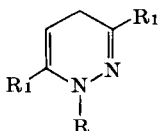
<sup>235</sup> V. Sprio and P. Madonia, *Ann. Chim. (Rome)* **48**, 1316 (1958).

<sup>236</sup> T. Ajello, V. Sprio, and G. Vaccaro, *Gazz. Chim. Ital.* **89**, 2232 (1959).

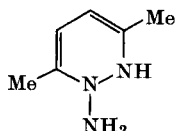
between hydrazine and a di- or polysubstituted saturated 1,4-diketone bearing aliphatic,<sup>237-244</sup> aryl,<sup>226, 244-249</sup> or mixed aryl and aliphatic or arylalkyl<sup>244, 246, 250</sup> and heterocyclic and aliphatic groups.<sup>251, 252</sup> Some 4,5-dihydropyridazines (15) are not particularly stable and are dehydrogenated in the presence of air or during distillation into the more stable pyridazines. Likewise, dehydrohalogenation has been observed,<sup>253</sup> and water is split off when using 2-hydroxy-1,4-diketones<sup>56</sup> as starting material.



(15)



(16)



(17)

On the other hand, 1,4-dihydropyridazines (16) are formed from a saturated 1,4-diketone<sup>239, 254</sup> or 1,4-dialdehyde<sup>255, 256</sup> and a monosubstituted hydrazine or semicarbazide (16, R = Ar, H, or

<sup>237</sup> K. Alder and C. H. Schmidt, *Chem. Ber.* **76B**, 183 (1943).

<sup>238</sup> E. E. Blaise, *Compt. Rend.* **170**, 1324 (1920).

<sup>239</sup> C. G. Overberger, N. R. Byrd, and R. R. Mesrobian, *J. Am. Chem. Soc.* **78**, 1961 (1956).

<sup>240</sup> R. G. Jones, *J. Org. Chem.* **25**, 956 (1960).

<sup>241</sup> G. Korschun, *Chem. Ber.* **37**, 2183 (1904).

<sup>242</sup> G. Korschun and C. Roll, *Gazz. Chim. Ital.* **41**, 186 (1911).

<sup>243</sup> B. G. Zimmerman and H. L. Lochte, *J. Am. Chem. Soc.* **60**, 2456 (1938).

<sup>244</sup> C. Paal and E. Dencks, *Chem. Ber.* **36**, 491 (1903).

<sup>245</sup> C. L. Arcus and P. A. Hallgarten, *J. Chem. Soc.*, 3407 (1957).

<sup>246</sup> W. Borsche and A. Klein, *Ann. Chem.* **548**, 74 (1941).

<sup>247</sup> S. Capuano, *Gazz. Chim. Ital.* **68**, 521 (1938).

<sup>248</sup> C. Paal and G. Kühn, *Chem. Ber.* **40**, 4598 (1907).

<sup>249</sup> S. G. Cohen, S. H. Hsiao, E. Saklad, and C. H. Wang, *J. Am. Chem. Soc.* **79**, 4400 (1957).

<sup>250</sup> C. Bülow and H. Filehner, *Chem. Ber.* **41**, 1886 (1908).

<sup>251</sup> S. Fatutta, *Ann. Chim. (Rome)* **51**, 252 (1961).

<sup>252</sup> S. Fatutta, *Ann. Chim. (Rome)* **52**, 365 (1962).

<sup>253</sup> C. Paal and H. Schulze, *Chem. Ber.* **35**, 168 (1902).

<sup>254</sup> W. Borsche and M. Spannagel, *Ann. Chem.* **331**, 298 (1904).

<sup>255</sup> W. Schlenk, H. Hillemann, and J. Rodloff, *Ann. Chem.* **487**, 135 (1931).

<sup>256</sup> D. Desaty, O. Hadžija, and D. Keglević, *Croat. Chem. Acta* **37**, 227 (1965).

$\text{CONH}_2$ ),<sup>254, 257</sup> or from 1,4-ketoaldehydes and monosubstituted hydrazines.<sup>258-261</sup>

However, not all reactions with saturated 1,4-diketones proceed as simply as assumed. With acetonylacetone<sup>238, 239</sup> or 1,2-dibenzoyl-ethane,<sup>244, 249</sup> disproportionation leads to a mixture of the corresponding pyridazine and tetrahydropyridazine. Different reaction conditions may also influence the reaction course. Thus, acetonylacetone can yield 3,6-dimethylpyridazine<sup>243</sup> and/or its tetrahydro analog<sup>239</sup> or with excess hydrazine a compound formulated as (17).<sup>262, 263</sup> Acetonylacetone, when treated with HCN to form a biscyanhydrin followed by treatment with hydrazine, gives 3,6-dimethyl-6-cyano-1,4,5,6-tetrahydropyridazine.<sup>264, 265</sup> Oxidation of the latter yields 3,6-dimethylpyridazine. The related diacetopropionic acid has been likewise reported to yield, besides the expected 3,6-dimethyl-4,5-dihydro-4-pyridazinecarboxylic acid, a derivative of pyrrole<sup>266</sup> or furan.<sup>241</sup>

### C. FROM 1,2-DICARBONYL COMPOUNDS

A very useful synthesis of 3(2*H*)-pyridazinones (18), comprising a multicomponent system, has been developed by Schmidt and Druey.<sup>105, 267, 268</sup> Although the reaction can be performed as a one-step condensation between a 1,2-dicarbonyl compound, an ester with a reactive  $\alpha$ -methylene group, and a monosubstituted or unsubstituted

<sup>257</sup> V. Sprio, P. Madonia, and I. Fabra, *Atti Accad. Sci., Lettere Arti Palermo, Pt. I* [4] **21**, 117 (1962); *Chem. Abstr.* **58**, 11354 (1963).

<sup>258</sup> C. Harries, *Chem. Ber.* **31**, 37 (1898).

<sup>259</sup> G. O. Schenck, *Ann. Chem.* **584**, 156 (1953).

<sup>260</sup> M. Verzele and F. Govaert, *Bull. Soc. Chim. Belges* **58**, 432 (1949).

<sup>261</sup> B. Helferich and O. Lecher, *Chem. Ber.* **54B**, 930 (1921).

<sup>262</sup> N. A. Domnin, M. N. Zelenina, and N. S. Glebovskaya, *Zh. Obshch. Khim.* **27**, 1516 (1957).

<sup>263</sup> N. A. Domnin, M. N. Zelenina, and N. S. Glebovskaya, *Zh. Obshch. Khim.* **27**, 2088 (1957).

<sup>264</sup> T. Bacchetti, *Gazz. Chim. Ital.* **80**, 783 (1950).

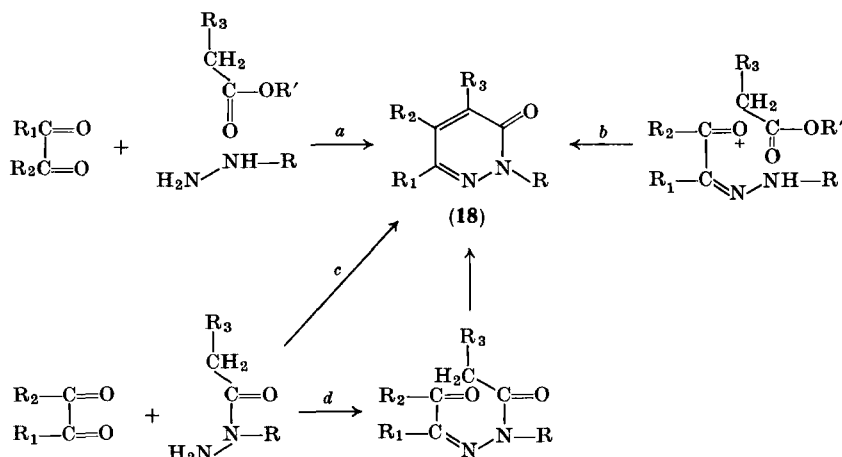
<sup>265</sup> C. G. Overberger, T. B. Gibb, S. Chibnik, Pao-Tung Huang, and J. J. Monagle, *J. Am. Chem. Soc.* **74**, 3290 (1952).

<sup>266</sup> N. M. Timoshevskaya, *Tr. Kharkovsk. Politekhn. Inst., Ser. Khim. Tekhnol.* **4**, 73 (1954); *Chem. Abstr.* **52**, 7279 (1958).

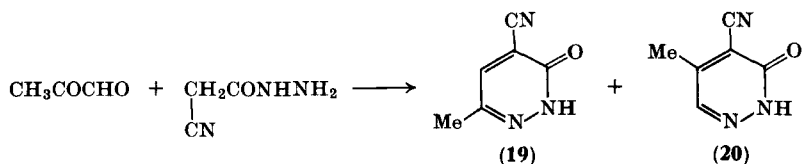
<sup>267</sup> P. Schmidt and J. Druey, *Helv. Chim. Acta* **37**, 134 (1954).

<sup>268</sup> P. Schmidt and J. Druey, *Helv. Chim. Acta* **37**, 1467 (1954).

hydrazine (path *a*), the preferred synthetic route is the condensation of two components to form the pyridazine ring. Thus, a mono-hydrazone of the 1,2-diketone is first prepared, in particular when aromatic diketones are used, and this is further condensed with the appropriate ester (path *b*). Alternatively, the acid hydrazide is condensed with the diketone and in the presence of sodium ethoxide the pyridazinone is formed directly (path *c*), whereas in the absence of



this reagent the hydrazone is formed (path *d*), which is then cyclized in a separate step. These last possibilities are particularly valuable when using aliphatic 1,2-dicarbonyl compounds as starting materials. Besides the basic condensing agents glacial acetic acid-ammonium acetate has also been used.

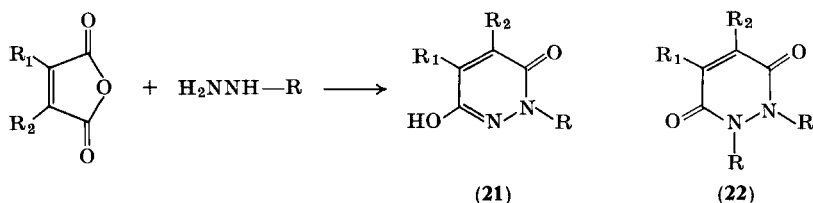


The dicarbonyl compounds used in these syntheses comprise 1,2-diketones,  $\alpha$ -ketoacids, or glyoxal, and esters with a reactive  $\alpha$ -methylene group are represented by malonic, acetoacetic, cyanoacetic, benzoylacetic, or hippuric esters. Many 4-, 5-, and/or 6-substituted 3(2*H*)-pyridazinones have thus been synthesized in reasonable yields.

With unsymmetrically substituted 1,2-dicarbonyl compounds the reaction, following routes *c* or *d*, might afford isomeric reaction products. This has been in fact established when condensing methylglyoxal with cyanoacethydrazide. The isomeric 6-methyl (**19**) and 5-methyl (**20**) derivatives were obtained in a 2:1 ratio.<sup>268</sup>

#### D. FROM ANHYDRIDES OF 1,2-DICARBOXYLIC ACIDS AND RELATED COMPOUNDS

One of the most common and versatile methods for the synthesis of polyfunctional pyridazines consists in the formation of the diazine ring from maleic anhydride or its mono- and disubstituted analogs and an unsubstituted, mono-, or disubstituted hydrazine. Pyridazinones of the types **21** and **22** are obtained in good yields.

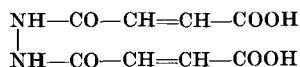


The reaction has been thoroughly investigated, especially with regard to reaction conditions, as it has been observed that different by-products can be formed. There is a marked effect of the reaction medium on the condensation between maleic anhydride and hydrazine. For instance, if hydrazine hydrate is added to 2 moles of the anhydride in acetic acid, the linear hydrazide (**23**) is formed. In ether or alcohol as solvent a mixture of products is formed and besides **23** the formation of the monohydrazide (**24**) has been assumed,<sup>23, 269</sup> as this upon heating is transformed into maleic hydrazide (**21**, R = R<sub>1</sub> = R<sub>2</sub> = H). Likewise, **23** is converted into maleic hydrazide and maleic acid at elevated temperature, and moreover this reaction occurs in aqueous solution. Another possible reaction product, *N*-aminomaleimide (**25**, R = R<sub>1</sub> = R<sub>2</sub> = H) or analogs, was reported first by Curtius<sup>270</sup>; although later workers reported failure to obtain these compounds,<sup>269</sup>

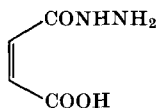
<sup>269</sup> H. Feuer, E. H. White, and J. E. Wyman, *J. Am. Chem. Soc.* **80**, 3790 (1958).

<sup>270</sup> T. Curtius and M. A. Foersterling, *J. Prakt. Chem.* [2] **51**, 371 (1895).

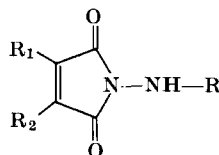
they have been established as the major products when condensing maleic or citraconic anhydride with phenylhydrazine in acetic acid.<sup>271-274</sup> Under similar reaction conditions **25**, ( $R_1 = H$ ,  $R_2 = Cl$ ,  $R = Ph$ ) is formed as a by-product in the case of chloromaleic anhydride,<sup>275</sup> whereas dimethylmaleic anhydride has been claimed to give only **25** and no pyridazine.<sup>273</sup> However, when the last-mentioned reaction is performed in benzene solution the corresponding pyridazinone can be isolated in low yield.<sup>126</sup>



(23)

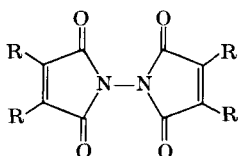


(24)

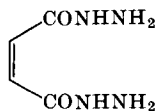


(25)

In another reaction, conducted also in acetic acid, methylmaleic hydrazide (**21**,  $R = R_2 = H$ ,  $R_1 = Me$ ) has been isolated as the only product.<sup>276</sup> If, however, a mixture of acetic acid and methanol were employed as solvent, citraconic and related anhydrides formed linear dihydrazides of type **23**.<sup>276</sup> A new type of reaction product, a  $N,N'$ -biimide (**26**), has been established to result when dimethyl- or dichloromaleic anhydride were allowed to react with hydrazine in acetic acid with cooling.<sup>276</sup>



(26)



(27)

<sup>271</sup> F. D. Chattaway and D. W. Parkes, *J. Chem. Soc.* **121**, 283 (1922).

<sup>272</sup> J. Druey, A. Hüni, K. Meier, B. H. Ringier, and A. Staehelin, *Helv. Chim. Acta* **37**, 510 (1954).

<sup>273</sup> K. Mori, *Yakugaku Zasshi* **82**, 1161 (1962).

<sup>274</sup> L. H. Flott and W. H. Gardner, "Maleic Anhydride Derivatives," p. 130. Wiley, New York, 1952.

<sup>275</sup> K. Meier, B. H. Ringier, and J. Druey, *Helv. Chim. Acta* **37**, 523 (1954).

<sup>276</sup> E. Hedaya, R. L. Hinman, and S. Theodoropoulos, *J. Org. Chem.* **31**, 1317 (1966).

The formation of *N*-aminomaleimides can be suppressed in strongly acidic aqueous solutions<sup>126, 274, 277</sup> or they can be rearranged into **21** upon heating with a base, mineral or acetic acid, or solvent.<sup>126, 273, 278, 279</sup> This rearrangement is reported to occur more readily with those maleimides possessing a more basic amino nitrogen.<sup>279</sup> Hydrazine salts of mineral acids favor the formation of **21**.<sup>23, 277, 280</sup>

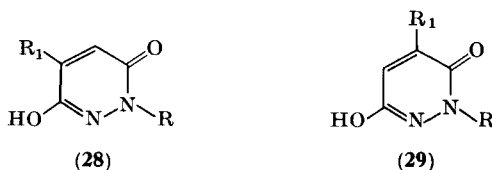
The steric effect<sup>126, 281</sup> has an important influence on pyridazine formation. This is particularly the case when the double bond of the anhydride is incorporated in a cyclic system, or with cyclic 1,2 diesters. At least four types of products can be produced and they were identified as a monohydrazide as **24**, a dihydrazide as **27**, an *N*-aminomaleimide derivative as **25**, or a pyridazinone as **21**. The dihydrazides are relatively easily converted into pyridazinones when heated with excess hydrazine or in dilute hydrochloric acid,<sup>281</sup> and treatment with nitrous acid has the same effect.<sup>282, 283</sup>

The literature contains many examples of pyridazinones of type **21** or **22** prepared from maleic,<sup>23, 269, 270, 272, 280, 284–293</sup> citraconic

- <sup>277</sup> R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.* **76**, 2201 (1954).  
<sup>278</sup> H. Feuer and H. Rubinstein, *J. Am. Chem. Soc.* **80**, 5873 (1958).  
<sup>279</sup> H. Feuer and J. P. Asunskis, *J. Org. Chem.* **27**, 4684 (1962).  
<sup>280</sup> Yu. A. Baskakov, and N. N. Mel'nikov, *Zh. Obshch. Khim.* **24**, 1216 (1954).  
<sup>281</sup> R. G. Jones, *J. Am. Chem. Soc.* **78**, 159 (1956).  
<sup>282</sup> M. Freri, *Gazz. Chim. Ital.* **66**, 23 (1936).  
<sup>283</sup> R. Otto and G. Holst, *J. Prakt. Chem.* [2] **42**, 65 (1890).  
<sup>284</sup> F. Arndt, L. Loewe, and L. Ergener, *Rev. Fac. Sci. Univ. Istanbul* **13A**, 103 (1948).  
<sup>285</sup> E. Dunkels and S. Hillers, *Latvijas PSR Zinatnu Akad. Vestis*, 105 (1954); *Chem. Abstr.* **49**, 9659 (1955).  
<sup>286</sup> P. Rapoš, J. Synak, and P. Winternitz, *Chem. Zvesti* **19**, 403 (1965).  
<sup>287</sup> A. N. Kost, A. A. Shumakova, E. I. Kozlova, and I. I. Grandberg, *Vestn. Mosk. Univ., Ser. Mat., Mekhan., Astron., Fiz. i. Khim.* **14**, 205 (1959); *Chem. Abstr.* **54**, 14553 (1960).  
<sup>288</sup> J. Druey, K. Meier, and A. Staehelin, *Helv. Chim. Acta* **45**, 1485 (1962).  
<sup>289</sup> Z. Proczdzicki and A. Chrzaszczewska, *Lodz. Towarz. Nauk: Wydzial III, Acta Chim.* **10**, 109 (1965); *Chem. Abstr.* **65**, 13697 (1966).  
<sup>290</sup> M. Sulzbacher, *Mfg. Chemist* **33**, 191 (1962).  
<sup>291</sup> K. Eichenberger, A. Staehelin, and J. Druey, *Helv. Chim. Acta* **37**, 837 (1954).  
<sup>292</sup> N. Takahayashi, *J. Pharm. Soc. Japan* **75**, 778 (1955).  
<sup>293</sup> H. Feuer and R. Harmetz, *J. Am. Chem. Soc.* **80**, 5877 (1958).

(methylmaleic) or itaconic,<sup>273, 276, 277, 280, 294-296</sup> dimethylmaleic,<sup>126, 273</sup> methylethylmaleic or phenylmaleic,<sup>116</sup> chloromaleic,<sup>275, 277, 280, 286, 295, 297</sup> bromomaleic,<sup>275, 280</sup> dichloro- or dibromomaleic<sup>280, 286, 297a</sup> anhydride, or steroid-maleic anhydride adducts.<sup>298</sup> Besides direct conversion, hydrazides can be formed and these have been transformed into pyridazinones by heating in a solvent<sup>271, 272</sup> or in the presence of an acid or its anhydride.<sup>272, 278, 279, 288</sup>

The reaction between a monosubstituted maleic anhydride and a monosubstituted hydrazine can give two possible pyridazinone isomers, **28** or **29**. The reaction between citraconic anhydride and



phenylhydrazine gives the isomers in nearly the same amount and in addition the substituted maleimide was isolated.<sup>272</sup> Chloromaleic anhydride and phenylhydrazine have been reported to give as the major product the 5-chloro isomer (**28**, R = Ph, R<sub>1</sub> = Cl) and the other isomer (**29**, R = Ph, R<sub>1</sub> = Cl) and the substituted maleimide in smaller amount.<sup>275</sup> With methylhydrazine, the 4-chloro isomer is formed in somewhat greater quantity.<sup>297, 299</sup> Bromomaleic anhydride also yields both isomers, the 5-bromo isomer predominating.<sup>275</sup>

The condensation of *cis*-aconitic anhydride with hydrazine forms the expected carboxymethyl pyridazinone (**28**, R = H, R<sub>1</sub> = CH<sub>2</sub>COOH).<sup>277</sup> Phenylhydrazine, however, yielded a mixture of the related pyridazinone and the monophenylhydrazide of citraconic

<sup>294</sup> H. Akashi, *Kogyo Kagaku Zasshi* **66**, 124 (1963); *Chem. Abstr.* **59**, 7525 (1963).

<sup>295</sup> D. Stefanye and W. L. Howard, *J. Org. Chem.* **19**, 115 (1954).

<sup>296</sup> S. Linholter, A. B. Kristensen, R. Rosenoern, S. E. Nelsen, and H. Kaaber, *Acta Chem. Scand.* **15**, 1660 (1961).

<sup>297</sup> Y. Maki, M. Takaya, and M. Suzuki, *Yakugaku Zasshi* **86**, 487 (1966).

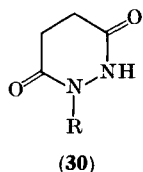
<sup>297a</sup> P. Ruggli and C. Hartmann, *Helv. Chim. Acta* **3**, 493 (1920).

<sup>298</sup> K. Schubert and K. H. Böhme, *Chem. Ber.* **93**, 1884 (1960).

<sup>299</sup> T. Nakagome, A. Misaki, and T. Komatsu, *Chem. Pharm. Bull. (Tokyo)* **14**, 1082 (1966).



acid. The formation of the latter product indicates that partial decarboxylation had occurred; it can be cyclized to methylmaleic phenylhydrazide (**28**,  $R = Ph$ ,  $R_1 = Me$ ), which can be in turn prepared from citraconic anhydride and phenylhydrazine or by decarboxylating **28** ( $R = Ph$ ,  $R_1 = CH_2COOH$ ).<sup>300</sup>



The saturated analogs, e.g., succinic anhydride or succinic esters, behave differently and only in few cases were pyridazines obtained. The reaction between succinic anhydride and various amounts of hydrazine hydrate has been studied under different reaction conditions, but always uncyclized products were formed.<sup>301</sup> One of these is a polymeric hydrazide which, when treated with benzenesulfonyl chloride, yielded the monobenzenesulfonyl derivative of cyclic succinhydrazide (**30**,  $R = PhSO_2$ ) along with a compound formulated as bicyclic disuccinhydrazide (**152**, Section IV, H, 4), but later shown to be **153**. Authentic cyclic succinhydrazide (**30**,  $R = H$ ) was obtained upon reducing maleic hydrazide with aluminum amalgam.<sup>301, 302</sup> Previous claims that **30** ( $R = H$ ) may be obtained from succinic acid or *N*-aminosuccinimide<sup>303, 304</sup> proved to be incorrect.

Much controversy has arisen when interpreting the reaction products between diethylsuccinate or its monoacylated analogs and hydrazines, the products being formulated as derivatives of pyrazolone or pyridazinone.<sup>112, 132, 135, 305, 306</sup> The structure of none of these products was proved. A reinvestigation of these reactions, using diethylformylsuccinate, diethylacetylsuccinate, and triethyloxalylsuccinate, showed that from each of these reactions a mixture of

<sup>300</sup> A. Krbavčič and M. Tišler, *Monatsh. Chem.* **97**, 644 (1966).

<sup>301</sup> H. Feuer, G. B. Bachman, and E. H. White, *J. Am. Chem. Soc.* **73**, 4716 (1951).

<sup>302</sup> R. L. Hinman and R. J. Landborg, *J. Org. Chem.* **24**, 724 (1959).

<sup>303</sup> T. Curtius, *J. Prakt. Chem.* [2] **92**, 74 (1915).

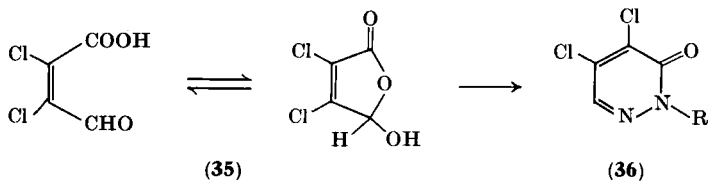
<sup>304</sup> E. Sernagiotto and M. D. Paravagno, *Gazz. Chim. Ital.* **44**, I, 538 (1914).

<sup>305</sup> R. Rothenburg, *J. Prakt. Chem.* [2], **51**, 140 (1895).

<sup>306</sup> A. Sonn, *Ann. Chem.* **518**, 290 (1935).



$\beta$ -formylacrylic acids have been used recently because 4,5-dihalo-pyridazinones (36) are obtained directly and are, because of their reactive halogens, very useful intermediates for further transformations. The reaction proceeds easily with hydrazine or monosubstituted hydrazines and the intermediate hydrazones are difficult to isolate as they cyclize readily.



Halogenated pyridazinones have been thus prepared from mucochloric acid (35),<sup>286, 312-316</sup> mucobromic acid,<sup>115, 287, 316-318</sup> or the related chlorobromo acid.<sup>286, 319</sup> Instead of hydrazine semicarbazide can be used and the intermediate semicarbazone cyclized in hot acetic acid, loss of the carbamido group taking place simultaneously.<sup>312, 318</sup> Acid hydrazides likewise form hydrazones first, which cyclize with the aid of phosphorus oxychloride.<sup>318</sup> Tosylhydrazones are reported to cyclize easily.<sup>3</sup>

## F. USE OF THE DIELS-ALDER REACTION

Pyridazines, particularly 1,2,3,6-tetrahydropyridazines (38), can be prepared via the Diels-Alder reaction. This is a good synthetic route for obtaining various alkyl- or aryl-substituted pyridazines. The most used dienophile for tetrahydropyridazine syntheses is a

<sup>312</sup> D. T. Mowry, *J. Am. Chem. Soc.* **75**, 1909 (1953).

<sup>313</sup> T. Kuraishi, *Pharm. Bull. (Tokyo)* **4**, 497 (1956).

<sup>314</sup> R. F. Homer, H. Gregory, and L. F. Wiggins, *J. Chem. Soc.*, 2191 (1948).

<sup>315</sup> P. Coad and R. A. Coad, *J. Org. Chem.* **28**, 1919 (1963).

<sup>316</sup> N. P. Buu-Hoi, R. Rips, and R. Royer, *Experientia* **12**, 212 (1956).

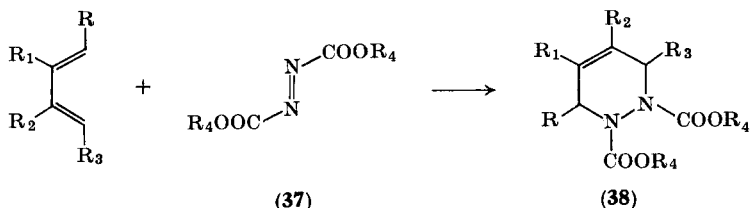
<sup>317</sup> A. Bistrzycki and H. Simonis, *Chem. Ber.* **32**, 534 (1899).

<sup>318</sup> A. Bistrzycki and C. Herbst, *Chem. Ber.* **34**, 1010 (1901).

<sup>319</sup> T. Kuraishi, *Chem. Pharm. Bull. (Tokyo)* **6**, 641 (1958).

dialkylazodicarboxylate (37), and in spite of its most likely trans configuration it reacts easily with simple conjugated dienes in 1,4 addition.<sup>249, 320-336</sup>

In addition to the normal 1,4 addition, dialkylazodicarboxylates can add to dienes by the "allylic addition." The reaction has been thoroughly investigated. Steric factors influence the reaction course as is evident in the case of dienes which are highly substituted at



<sup>320</sup> O. Diels, J. H. Blom, and W. Koll, *Ann. Chem.* **443**, 242 (1925).

<sup>321</sup> K. Alder, H. Niklas, R. Aumüller, and B. Olsen, *Ann. Chem.* **585**, 81 (1954).

<sup>322</sup> C. H. Wang, S. Hsiao, E. Saklad, and S. G. Cohen, *J. Am. Chem. Soc.* **79**, 2661 (1957).

<sup>323</sup> V. R. Skvarchenko, M. G. Kuz'min, and R. Ya. Levina, *Vestn. Mosk. Univ., Ser. Mat., Mekhan., Astron., Fiz. i. Khim.* **12**, 169 (1957); *Chem. Abstr.* **52**, 6358 (1958).

<sup>324</sup> Yu. S. Shabarov, R. Ya. Levina, N. I. Vasil'ev, and N. A. Vasilenko, *Zh. Obshch. Khim.* **31**, 378 (1961).

<sup>325</sup> J. C. J. Mackenzie, A. Rodgman, and G. F. Wright, *J. Org. Chem.* **17**, 1666 (1952).

<sup>326</sup> J. Levisalles and P. Baranger, *Compt. Rend.* **238**, 592 (1954).

<sup>327</sup> R. Ya. Levina, Yu. S. Shabarov, M. G. Kuz'min, N. I. Vasil'ev, S. I. Pokraka, and E. G. Treshchova, *Zh. Obshch. Khim.* **29**, 3541 (1959).

<sup>328</sup> S. G. Cohen and R. Zand, *J. Am. Chem. Soc.* **84**, 586 (1962).

<sup>329</sup> P. Baranger, J. Levisalles, and M. Vuidart, *Compt. Rend.* **236**, 1365 (1953).

<sup>330</sup> P. Baranger and J. Levisalles, *Bull. Soc. Chim. France*, 704 (1957).

<sup>331</sup> O. Diels and K. Alder, *Ann. Chem.* **450**, 237 (1926).

<sup>332</sup> B. T. Gillis and P. E. Beck, *J. Org. Chem.* **27**, 1947 (1962).

<sup>333</sup> L. A. Carpino, P. H. Terry, and S. D. Thatte, *J. Org. Chem.* **31**, 2867 (1966).

<sup>334</sup> Yu. S. Shabarov, N. I. Vasil'ev, and R. Ya. Levina, *Dokl. Akad. Nauk SSSR* **129**, 600 (1959).

<sup>335</sup> R. Ya. Levina, Yu. S. Shabarov, M. G. Kuz'min, N. I. Vasil'ev, and E. G. Treshchova, *Dokl. Akad. Nauk SSSR* **121**, 303 (1958).

<sup>336</sup> H. R. Snyder and J. G. Michels, *J. Org. Chem.* **28**, 1144 (1963).

positions 1 and 4, e.g., 2,5-dimethylhexa-2,4-diene and 2,4-dimethylpenta-1,3-diene.<sup>332, 337, 338</sup> Here the normal Diels–Alder reaction is prevented and addition takes place by other pathways.<sup>332</sup> Also furans, when used as dienes, do not afford the desired pyridazines.<sup>330</sup> Other factors which influence the reaction rate were summarized recently in a review on  $\alpha$ -carbonyl azo compounds.<sup>339</sup>

Instead of **37** other azo compounds can be used, giving the same type of pyridazines. Use of fluoroazoalkanes,<sup>340</sup> azodicarbonitrile,<sup>341</sup> azobisformamidine dinitrate,<sup>325</sup> azodiaroyls,<sup>334, 337</sup> and even aromatic azo compounds<sup>329</sup> at elevated temperatures is reported. An investigation into the scope of the reaction revealed that the  $\text{—N=N—C=C—}$  system is not able to react as a diene to form pyridazines.<sup>342</sup>

### G. FROM FURANS

Pyridazines have been prepared from furans and their reduced analogs. One of the most investigated reactions was introduced by Clauson–Kaas. Furans are treated with bromine in methanolic solution to give derivatives of 2,5-dihydrofuran (**39**). These are then submitted to acid hydrolysis and the intermediate en-dione (**40**) (or the aldehydic analog) reacts with hydrazine to form the corresponding pyridazine (**41**).<sup>17, 18, 220, 343–348</sup> The intermediate **40** should have the *cis* configuration. The overall yields are not high and the reaction does not form tri- or tetraalkylpyridazines<sup>343</sup> because of steric factors.

<sup>337</sup> Yu. S. Shabarov, N. I. Vasil'ev, I. S. Levina, and R. Ya. Levina, *Zh. Obshch. Khim.* **32**, 2806 (1962).

<sup>338</sup> B. T. Gillis and P. E. Beck, *J. Org. Chem.* **28**, 3177 (1963).

<sup>339</sup> E. Fahr and H. Lind, *Angew. Chem.* **78**, 376 (1966).

<sup>340</sup> W. J. Chambers, C. W. Tullock, and D. D. Coffman, *J. Am. Chem. Soc.* **84**, 2337 (1962).

<sup>341</sup> F. D. Marsh and M. E. Hermes, *J. Am. Chem. Soc.* **87**, 1819 (1965).

<sup>342</sup> J. van Alphen, *Rec. Trav. Chim.* **64**, 109 (1945).

<sup>343</sup> J. Levisalles, *Bull. Soc. Chim. France*, 997 (1957).

<sup>344</sup> M. Robba, *Ann. Chim. (Paris)* [13] **5**, 351 (1960).

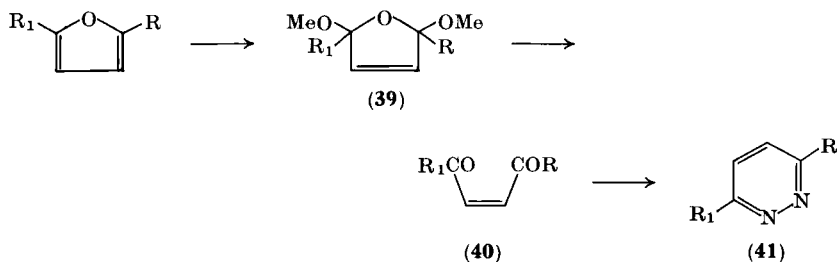
<sup>345</sup> N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.* **1**, 619 (1947).

<sup>346</sup> W. R. Edwards and M. J. Mitchell, *J. Am. Chem. Soc.* **76**, 5150 (1954).

<sup>347</sup> N. Elming, *Acta Chem. Scand.* **6**, 572 (1952).

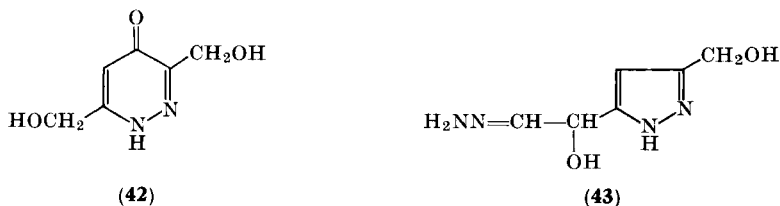
<sup>348</sup> J. Fakstorp, D. Raleigh, and L. E. Schniepp, *J. Am. Chem. Soc.* **72**, 869 (1950).

3,6-Dimethylpyridazine has been reported to result from one of the three different 2,5-dimethylfuran bishydroperoxides and hydrazine<sup>349</sup> and a derivative of tetrahydropyridazine was obtained from 2,5-diethoxytetrahydrofuran and tosylhydrazine.<sup>16</sup>



#### H. FROM PYRONES, TETRAZINES, AND OTHER HETEROCYCLES

In the pyrone series, kojic acid is transformed by hydrazine into 3,6-dihydroxymethyl-4(1*H*)-pyridazinone (42).<sup>350, 351</sup> In addition, a pyrazole (43) was isolated as by-product.<sup>351</sup> 5-Methylkojic acid reacted with hydrazine to give only the pyrazole derivative<sup>350</sup> and kojic acid and phenylhydrazine afforded a mixture of both types of compound.<sup>352</sup>



Another type of pyridazine synthesis from pyrones involves coupling of the latter with diazonium salts and rearrangement of the intermediate hydrazones with either aqueous base or acid to pyridazinones. Thus, 4-hydroxy-6-methyl-2-pyrone (triacetic lactone) (44)

<sup>349</sup> D. Seebach, *Chem. Ber.* **96**, 2712 (1963).

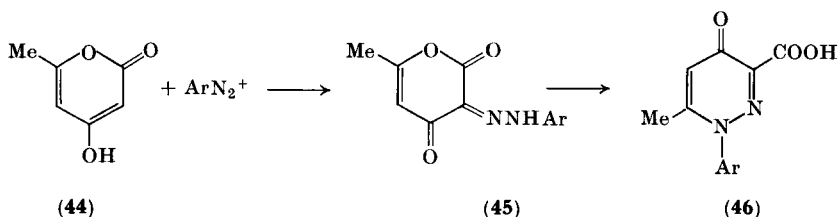
<sup>350</sup> R. Kotani and Ch. Tatsumi, *Bull. Univ. Osaka Prefect.* **B10**, 33 (1960); *Chem. Abstr.* **58**, 11318 (1963).

<sup>351</sup> A. F. Thomas and A. Marxer, *Helv. Chim. Acta* **41**, 1898 (1958).

<sup>352</sup> A. Marxer and A. F. Thomas, *Chimia (Aarau)* **14**, 126 (1960).

gives the hydrazones (45) which readily rearrange to 1-aryl-6-methyl-4-oxo-1,4-dihydropyridazine 3-carboxylic acids (46).<sup>353, 354</sup>

The isomeric 6-hydroxy-2-pyrone (glutaconic anhydride) and its 4-methyl analog (47) react similarly with aryldiazonium salts and on hydrolysis with dilute alkali or acid the hydrazones (48) are transformed into 1-aryl-6-oxo-1,6-dihydro-3-pyridazinecarboxylic acids or their 4-methyl analogs (49)<sup>355, 356</sup> in variable yields (28–74%).



The 4-methyl analogs have been obtained analogously from 6-hydroxy-2-pyridones (50). With diazonium salts hydrazones (51) are formed and these are converted by alkali into 49.<sup>357</sup> On the other hand, dimethyl- $\beta$ -methylglutaconate (52,  $\text{R} = \text{Me}$ ) was shown to undergo coupling with diazonium salts and to give a mixture of dimethyl- $\gamma$ -arylhydrazono- $\beta$ -methylglutaconate (53) and a pyridazinone (54). Both can be further converted by alkali into 49.<sup>357</sup>

Pyridazines are accessible from pyrrole derivatives by ring enlargement or by ring contraction of diazepinones. 4-Isonitroso-1,4-dihydropyridazines have been reported to result from the action of hydrazine on 3-isonitrosopyrroles,<sup>236, 358</sup> and *N*-aminopyrroles upon heating or treatment with acid rearrange to pyridazines.<sup>168, 359</sup> On the other hand, ring contraction of 1,2-diazepinones to pyridazines is recorded and the reaction has been formulated as a solvolytic displacement at the C-7 atom of the seven-membered ring.<sup>360, 361</sup>

<sup>353</sup> J. F. Morgan, *J. Am. Chem. Soc.* **70**, 2253 (1948).

<sup>354</sup> R. H. Wiley and C. H. Jarboe, *J. Am. Chem. Soc.* **78**, 624 (1956).

<sup>355</sup> R. H. Wiley and C. H. Jarboe, *J. Am. Chem. Soc.* **77**, 403 (1955).

<sup>356</sup> R. H. Wiley and H. G. Ellert, *J. Am. Chem. Soc.* **77**, 5187 (1955).

<sup>357</sup> R. H. Wiley and C. L. De Silva, *J. Am. Chem. Soc.* **78**, 4683 (1956).

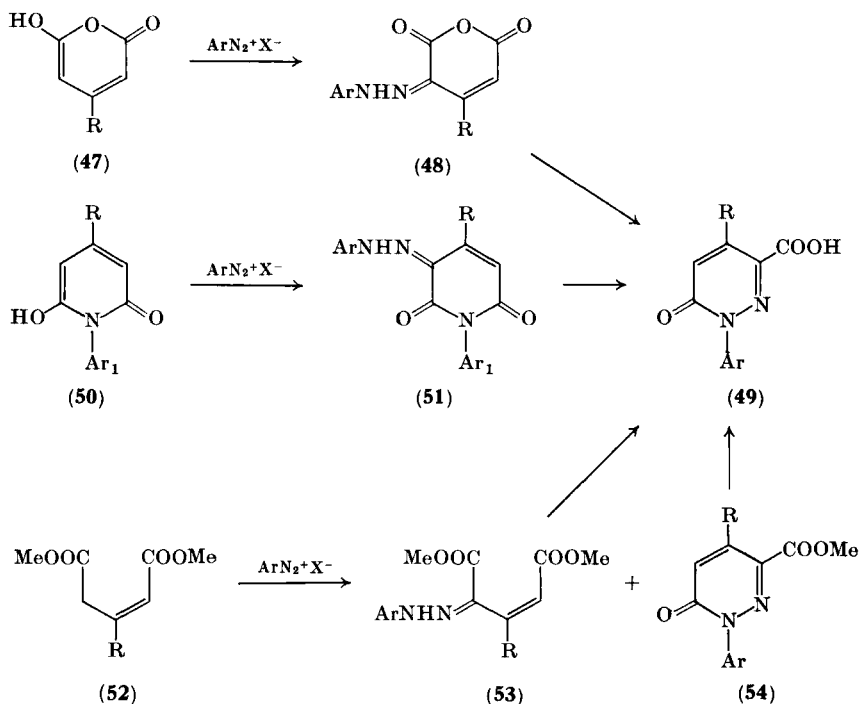
<sup>358</sup> T. Ajello, A. Miraglia, and R. Torcetta, *Gazz. Chim. Ital.* **77**, 525 (1947).

<sup>359</sup> D. M. Lemal and T. W. Rave, *J. Am. Chem. Soc.* **87**, 393 (1965).

<sup>360</sup> R. K. Bly, E. C. Zoll, and J. A. Moore, *J. Org. Chem.* **29**, 2128 (1964).

<sup>361</sup> J. A. Moore and W. J. Theuer, *J. Org. Chem.* **30**, 1887 (1965).

The first observation that 1,2,4,5-tetrazines (**55**) can be transformed into pyridazines was due to Carboni and Lindsey.<sup>362</sup> The reaction proceeds between tetrazines having strongly electrophilic substituents and a variety of ethylenic or acetylenic compounds<sup>362-365, 365a</sup> and is



formulated as a 1,4 addition of the diene system of the tetrazine to the appropriate dienophiles. Because of its ease, speed, and quantitative course in most cases, the reaction with 3,6-dicarbomethoxy-1,2,4,5-tetrazine was proposed as a titrimetric method for the determination

<sup>362</sup> R. A. Carboni and R. V. Lindsey, *J. Am. Chem. Soc.* **81**, 4342 (1959).

<sup>363</sup> W. A. Butte and F. H. Case, *J. Org. Chem.* **26**, 4690 (1961).

<sup>364</sup> J. Sauer, A. Mielert, D. Lang, and D. Peter, *Chem. Ber.* **98**, 1435 (1965).

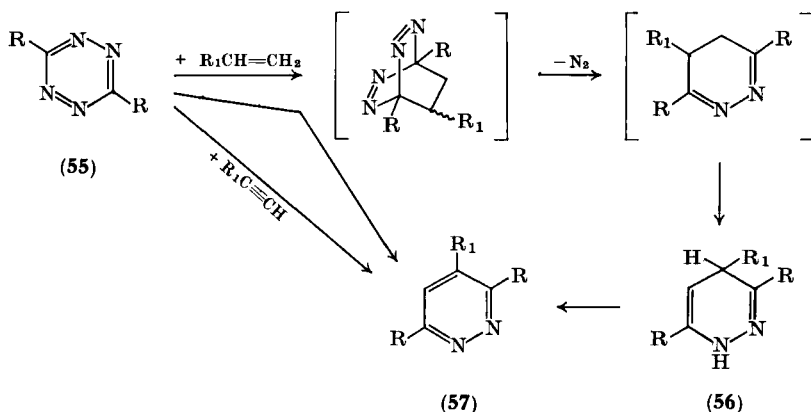
<sup>365</sup> M. Avram, J. G. Dinulescu, E. Marica, and C. D. Nenitzescu, *Chem. Ber.* **95**, 2248 (1962).

<sup>365a</sup> J. Sauer and G. Heinrichs, *Tetrahedron Letters*, 4979 (1966).



of olefins.<sup>365</sup> With simple ethylenic compounds dihydropyridazines (56) are formed and the uncertainty regarding their structure was removed by NMR investigations<sup>364, 366</sup> which clearly demonstrated the 1,4-dihydro structure.

These reduced pyridazines (56) are easily oxidized to pyridazines (57) and these can in turn be obtained directly from acetylenes and allenes or such ethylenic compounds as enol ethers, enol esters, enamines, or ketene diethylacetal.<sup>364</sup> Acetylenes exhibit a diminished



reactivity in comparison to ethylenic counterparts and yields are normally low. It has been further established that dienophiles with electron-releasing substituents facilitate the reaction whereas those with electron-attracting groups have the reverse effect. There are also steric effects which may be important for the reactivity of the dienophile.

### I. MISCELLANEOUS SYNTHESSES

There are numerous examples of pyridazine ring formation from a variety of starting materials. Most of these reactions do not represent synthetic approaches of general applicability and many of them were

<sup>366</sup> M. Avram, G. R. Bedford, and A. R. Katritzky, *Rec. Trav. Chim.* **82**, 1053 (1963).

discovered in connection with investigations on other aspects of chemistry. The structures of many of these products have not been firmly proved.

In addition to the foregoing 1,4-difunctional compounds used for cyclizations, the following have been used to give pyridazines or their reduced analogs: 1,4-hydroxyketones,<sup>367</sup> 1,4-haloketones,<sup>368-370</sup> 1,4-dibromobutane,<sup>302, 371-373</sup> 2,5-dibromohexane,<sup>374</sup> 1,4-haloesters,<sup>375</sup> or butadiene dioxide.<sup>376</sup> Hexahydropyridazine results as one of the oxidation products of 1,4-diaminobutane<sup>377</sup> and its 1-butyl analog is formed in the reduction of *N*-nitroso-4-chlorodibutylamine.<sup>378</sup>

Pyridazine can be obtained from its benzologs by oxidation. Thus, various cinnolines, phthalazines, or other polycycles afforded the corresponding pyridazinedicarboxylic or tetracarboxylic acids (see Section IV, E). Similarly, pyridazines with a fused three- or four-membered ring readily give substituted pyridazines upon ring opening.<sup>379-380</sup>

Other reactions to give pyridazines include addition of 1,1-dimethyldiazenium bromide to dienes,<sup>381, 382</sup> and addition of diazonium

<sup>367</sup> H. Ohle, M. Hielscher, and G. Noetzel, *Chem. Ber.* **76B**, 1051 (1943).

<sup>368</sup> J. B. Conant, J. B. Segur, and W. R. Kirner, *J. Am. Chem. Soc.* **46**, 1882 (1924).

<sup>369</sup> A. N. Kost, I. I. Grandberg, A. P. Terent'ev, and S. N. Milovanova, *Zh. Obshch. Khim.* **29**, 93 (1959).

<sup>370</sup> H. Wasserman and J. B. Brous, *J. Org. Chem.* **19**, 515 (1954).

<sup>371</sup> G. Zinner and W. Deucker, *Arch. Pharm.* **295**, 526 (1962).

<sup>372</sup> G. Wittig, W. Joos, and P. Rathfelder, *Ann. Chem.* **610**, 180 (1957).

<sup>373</sup> A. Zweig and A. K. Hoffmann, *J. Am. Chem. Soc.* **85**, 2736 (1963).

<sup>374</sup> C. G. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *J. Am. Chem. Soc.* **77**, 4100 (1955).

<sup>375</sup> H. Wohlgemuth, *Ann. Chim. (Paris)* [9] **2**, 403 (1914).

<sup>376</sup> R. Gabler and H. R. Meyer, *Angew. Chem.* **74**, 942 (1962).

<sup>377</sup> A. Lüttringhaus, J. Jander, and R. Schneider, *Chem. Ber.* **92**, 1756 (1959).

<sup>378</sup> S. Wawzonek and T. P. Culbertson, *J. Am. Chem. Soc.* **81**, 3367 (1959).

<sup>379</sup> G. Meier, *Angew. Chem.* **75**, 920 (1963).

<sup>380</sup> G. Meier, *Chem. Ber.* **99**, 1232 (1966).

<sup>381</sup> W. H. Urry, P. Szecsi, C. Ikoku, and D. W. Moore, *J. Am. Chem. Soc.* **86**, 2224 (1964).

<sup>382</sup> W. H. Urry, H. W. Kruse, and W. R. McBride, *J. Am. Chem. Soc.* **79**, 6568 (1957).

salts across two molecules of ketene diethylacetal.<sup>383</sup> Cycloaddition of diphenyl ketene to diethylazodicarboxylate has been claimed to give a pyridazine derivative,<sup>384</sup> but it was later shown<sup>385, 386</sup> that the product has a bicyclic structure. Cyclopropene or cyclopropenones form pyridazines with diazoalkanes<sup>387, 388</sup> and the latter also with hydrazine.<sup>389</sup> Further reactions leading to pyridazines are the decomposition of  $\omega$ -chloroacetophenone semicarbazone<sup>249, 390</sup> or acetophenone *N*-phenylbenzenesulfonyl hydrazone,<sup>391</sup> the isomerization of hydrazones formed in the Japp-Klingemann reaction of  $\gamma,\delta$ -unsaturated  $\beta$ -ketoesters,<sup>392</sup> and the decomposition of hydrazides of a  $\beta,\gamma$ -unsaturated acid.<sup>393</sup> They have also been reported to result from the reactions of  $\alpha$ -haloacetophenones and phenylhydrazine,<sup>394</sup> diethyl acetonedicarboxylate and diazonium salts,<sup>395</sup> acetylacetone and a hydrazone,<sup>395</sup> diethyl malonate and a bisazo compound,<sup>396</sup> diethyl oxalate and hydrazides,<sup>397</sup> 1,2,3,4-tetrabenzoyl cyclobutane and hydrazine,<sup>398</sup> benzonitrile and Grignard reagents,<sup>399</sup> and *p*-nitro-nitrosobenzene and a substituted butadiene.<sup>400</sup>

<sup>383</sup> S. M. McElvain and A. Jelinek, *J. Am. Chem. Soc.* **65**, 2236 (1943).

<sup>384</sup> C. K. Ingold and S. D. Weaver, *J. Chem. Soc.* **127**, 378 (1925).

<sup>385</sup> E. Fahr, K. H. Keil, F. Scheckenbach, and A. Jung, *Angew. Chem.* **76**, 579 (1964).

<sup>386</sup> E. Fahr, *Angew. Chem.* **76**, 505 (1964).

<sup>387</sup> K. B. Wiberg and W. J. Bartley, *J. Am. Chem. Soc.* **82**, 6375 (1960).

<sup>388</sup> P. T. Izzo and A. S. Kendo, *Chem. & Ind. (London)*, 839 (1964).

<sup>389</sup> R. Breslow, R. Boikess, and M. Battiste, *Tetrahedron Letters* No. 26, 42 (1960).

<sup>390</sup> A. P. J. Hoogeveen and C. W. van Hoogstraten, *Rec. Trav. Chim.* **52**, 378 (1933).

<sup>391</sup> A. Dornow and W. Bartsch, *Ann. Chem.* **602**, 23 (1957).

<sup>392</sup> D. Shapiro, R. A. Abramovitch, and S. Pinchas, *J. Am. Chem. Soc.* **78**, 2144 (1956).

<sup>393</sup> H. D. Stachel, *Arch. Pharm.* **295**, 224 (1962).

<sup>394</sup> D. Y. Curtin and E. W. Tristram, *J. Am. Chem. Soc.* **72**, 5238 (1950).

<sup>395</sup> W. Ried and G. Keil, *Ann. Chem.* **616**, 108 (1958).

<sup>396</sup> D. Vorländer, W. Zeh, and H. Enderlein, *Chem. Ber.* **60B**, 849 (1927).

<sup>397</sup> H. Hallmann, I. Ringhardt, and U. Fischer, *Chem. Ber.* **90**, 537 (1957).

<sup>398</sup> G. W. Griffin, R. B. Hager, and D. F. Veber, *J. Am. Chem. Soc.* **84**, 1008 (1962).

<sup>399</sup> E. Ectors, *Bull. Soc. Chim. Belges* **33**, 146 (1924).

<sup>400</sup> J. Hamer and R. E. Bernard, *J. Org. Chem.* **28**, 1405 (1963).

## IV. Reactions and Properties of Pyridazines

### A. ALKYL- AND ARYLPYRIDAZINES

This chapter is concerned only with *C*-alkyl- or arylpyridazines; for the *N*- and/or *O*-alkyl or aryl derivatives see Section IV, C. Alkyl- or arylpyridazines can be prepared, as outlined in Section III, from open-chain compounds, or frequently via the corresponding pyridazinones. These are converted into the 3-halo- or 3,6-dihalo-pyridazines (usually the chloropyridazines are obtained by the action of phosphorus oxychloride) and subsequent dehalogenation gives the desired pyridazine in reasonable yield. In the older literature dehalogenation involved phosphorus and hydroiodic acid, but now smooth catalytic hydrogenation in the presence of palladium on charcoal is preferred.<sup>116, 268, 401</sup> Dehalogenation of 3-chloro-6-methylpyridazine in the presence of Raney nickel is reported not to give good results.<sup>402</sup> Another possibility, as exemplified with 3-phenylpyridazine, is the desulfurization of the corresponding thiopyridazinone with Raney nickel.<sup>403</sup> The decarboxylation of alkyl- or arylpyridazinecarboxylic acids is also useful (Section IV, E).

Using one of the above methods the following substituted pyridazines have been synthesized: 3-methyl-,<sup>161, 345, 401, 402</sup> 4-methyl-,<sup>268, 277</sup> 3,4-dimethyl-,<sup>56, 126, 268</sup> 3,5-dimethyl-,<sup>116</sup> 3,6-dimethyl-,<sup>56, 220, 263, 349, 351, 404</sup> 4,5-dimethyl-,<sup>126</sup> 3,4,6-trimethyl-,<sup>56</sup> 3,4,5,6-tetramethyl-,<sup>56</sup> 3-ethyl-,<sup>116</sup> 3-methyl-4-(or 5- or 6-)ethyl-,<sup>56, 116</sup> 4-methyl-5-ethyl-,<sup>116</sup> 3,6-dimethyl-4-ethyl- and 3,4,6-trimethyl-,<sup>56</sup> 4-isopropyl-,<sup>347</sup> 3-*n*-pentyl-,<sup>116</sup> 3-phenyl-,<sup>11, 403</sup> 4-phenyl-,<sup>22, 116, 405</sup> 3,4-diphenyl-,<sup>139</sup> 3,5-diphenyl-,<sup>139, 370</sup> 3,6-diphenyl-,<sup>221-224, 229, 248, 406, 407</sup> 3,4,6-triphenyl-,<sup>230, 231</sup> 4-methyl-5-phenyl-,<sup>360</sup> 4-methyl-6-phenyl-,<sup>160</sup> and other 3-aryl-, 3-alkyl-6-aryl-, or 3,6-diarylpyridazines.<sup>56, 161, 222, 246</sup>

<sup>401</sup> M. Kumagai, *Nippon Kagaku Zasshi* **81**, 489 (1960); *Chem. Abstr.* **55**, 6487 (1961).

<sup>402</sup> W. G. Overend, L. M. Turton, and L. F. Wiggins, *J. Chem. Soc.*, 3500 (1950).

<sup>403</sup> G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 3789 (1959).

<sup>404</sup> C. Paal and J. Ueber, *Chem. Ber.* **36**, 497 (1903).

<sup>405</sup> R. Stoermer and H. Fincke, *Chem. Ber.* **42**, 3115 (1909).

<sup>406</sup> F. G. Baddar, A. El-Habashi, and A. K. Fateen, *J. Chem. Soc.*, 3342 (1965).

<sup>407</sup> P. Baumgartner and G. Hügel, *Bull. Soc. Chim. France*, 1005 (1954).

Pyridazine can be alkylated and arylated by the action of Grignard reagents or organolithium compounds at low temperatures. With Grignard reagents 4-substituted pyridazines are formed, the 4-phenyl derivative in low yield and 4-*n*-butylpyridazine in somewhat higher.<sup>408</sup> On the other hand, with lithium compounds 3-substituted pyridazines have been isolated and in higher yields than the products from the Grignard reactions. The solvent has a marked effect upon orientation; treatment of pyridazine with *n*-butyllithium in ether-tetrahydrofuran gives a mixture of 3- and 4-*n*-butylpyridazines.<sup>408</sup> If both *ortho* positions to the ring nitrogens are substituted as in 3,6-dimethoxy-pyridazine, the substituent enters the 4-position with both organo-metallic reagents.<sup>409</sup>

Various 4-(or 5-)alkylated or arylated dihydropyridazines have been prepared by the addition of Grignard reagents to 3,6-disubstituted pyridazines. The dihydropyridazines are then easily aromatized. It is known that in the reaction of Grignard reagents with azaaromatics both 1,2 and 1,4 addition, with respect to the hetero atom, may occur.<sup>410</sup> According to Gilman<sup>411</sup> these differences can be explained in terms of localization energies of the heterocycle and of the reactivity of the organometallic compound. Pyridazines react with Grignard reagents with conjugate addition to the C=C—C=N system and 4- or 5-alkyl- or aryl dihydropyridazines are obtained.<sup>169, 408, 409, 412, 413</sup>

Symmetrically 3,6-disubstituted pyridazines yield homogeneous 4-substituted products, but if the substituents are different the formation of two different 4- and 5-substituted products is expected and was observed when *tert*-butylmagnesium chloride was added to 3-methoxy-6-phenylpyridazine (**58**). The products were not separated, but the mixture was hydrolyzed with acid and the products were characterized as  $\alpha$ -*tert*-butyl- $\beta$ -benzoylpropionate (**60**) and 4-*tert*-butyl-3-phenyl-6-oxo-1,4,5,6-tetrahydropyridazine (**62**).<sup>169</sup> The ratio of the isomeric adducts is approximately 2:1 and the preponderance

<sup>408</sup> R. L. Letsinger and R. Lasco, *J. Org. Chem.* **21**, 812 (1956).

<sup>409</sup> I. Crossland, *Acta Chem. Scand.* **18**, 1653 (1964).

<sup>410</sup> M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," p. 1251. Prentice-Hall, Englewood Cliffs, New Jersey, 1954.

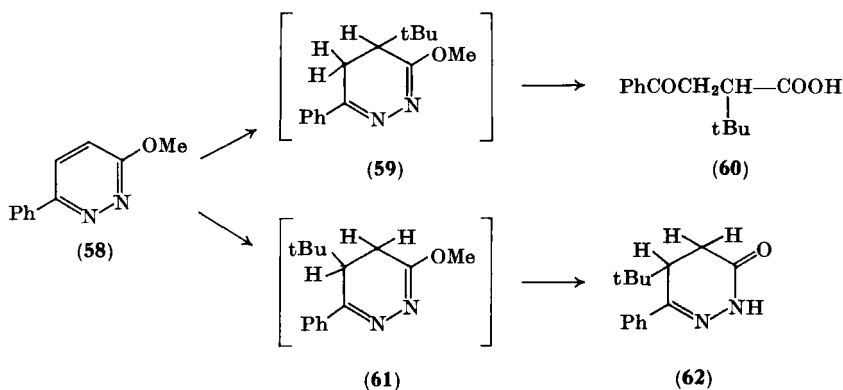
<sup>411</sup> H. Gilman, J. Eisch, and T. Soddy, *J. Am. Chem. Soc.* **79**, 1245 (1957).

<sup>412</sup> I. Crossland, *Acta Chem. Scand.* **16**, 1877 (1962).

<sup>413</sup> A. Christensen and I. Crossland, *Acta Chem. Scand.* **17**, 1276 (1963).

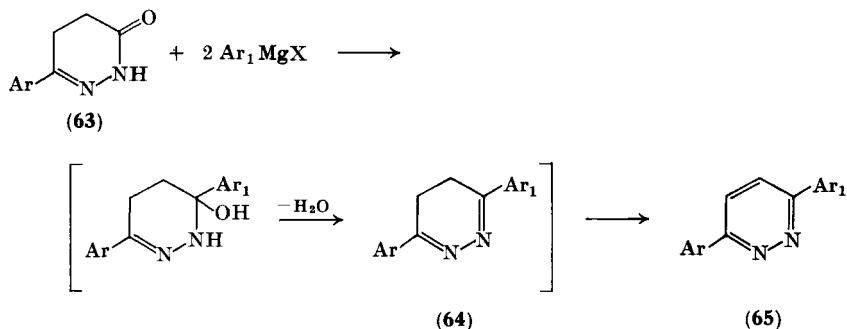
of **59** over **61** is explained in terms of the steric effect of the phenyl group and electronic effects of the Grignard reagent.

Arylation of 3-aryl-6-oxo-1,4,5,6-tetrahydropyridazines (**63**) with Grignard reagents has been similarly performed. It is believed that



4,5-dihydropyridazines (**64**) are formed and these dehydrogenate spontaneously to pyridazines (**65**).<sup>140, 406, 414</sup> The fully aromatic analogs, i.e., 6-aryl-3(2*H*)-pyridazinones, react by 1,4 addition and 4-arylated products are formed.<sup>406</sup>

Phenylations with reactions involving free radicals have also been carried out.<sup>415</sup> *N*-Nitrosoacetanilide as source of the phenyl radical



<sup>414</sup> A. Mustafa, W. Asker, A. H. Harhash, K. M. Foda, H. H. Jahine, and N. A. Kassab, *Tetrahedron* **20**, 531 (1964).

<sup>415</sup> C. M. Atkinson and C. J. Sharpe, *J. Chem. Soc.*, 3040 (1959).

produced 4-phenylpyridazine in best yield along with a small quantity of a diphenylpyridazine. There was no evidence of phenylation at positions adjacent to the ring nitrogens.

A particular case of the formation of 3,6-diphenylpyridazine is the extrusion of sulfur from 2,7-dihydro-3,6-diphenyl-1,4,5-thiadiazepine or its *S,S*-dioxide by means of *N*-bromosuccinimide.<sup>416</sup>

The ionization constants of different mono- or polyalkylated pyridazines<sup>56, 417, 418</sup> show that the number and position of the alkyl groups affect the basicity of these compounds. Alkyl groups cause an increase in the basicity of pyridazine, due to inductive effects. Dipole moments have also been determined.<sup>47</sup> The NMR spectrum of 3-methylpyridazine shows an ABX system in which  $J_{AB} \gg \delta_A - \delta_B$ , whereas spectrum of 4-methylpyridazine has been analyzed as an ABXY<sub>3</sub> system.<sup>86</sup> NMR studies on 3-phenylpyridazines suggested that the phenyl and pyridazine rings are coplanar and that coplanarity of the rings is not inhibited by the introduction of even a large substituent at the 5-position. However, an alkyl group in the 4-position of the pyridazine nucleus compels the rings to adopt an out-of-plane arrangement.<sup>419</sup>

Quaternization of 3- and 4-methylpyridazine with MeI has been reported<sup>277, 403</sup> to proceed at N<sub>2</sub> and N<sub>1</sub>, respectively. A later examination of the NMR spectra of the quaternized products disclosed that in each case a mixture of the N<sub>1</sub>- and N<sub>2</sub>-methylated isomers was formed.<sup>420</sup>

Methylpyridazines are oxidized to the corresponding acids (see Section IV, E). With selenium dioxide 3-methylpyridazine forms the 3-aldehyde.<sup>421</sup>

The resemblance of the 3- (and 4-)methyl group in pyridazine to that of 2-methylpyridine arises from its activation by the electron-attracting ring nitrogens with the possibility of formation of a comparatively stable anion. Thus, typical aldol-like condensations of 3-methylpyridazine, its 6-phenyl analog, and 4-methylpyridazine

<sup>416</sup> J. D. Loudon and L. B. Young, *J. Chem. Soc.*, 5496 (1963).

<sup>417</sup> A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).

<sup>418</sup> S. F. Mason, *J. Chem. Soc.*, 1247 (1959).

<sup>419</sup> I. Crossland, *Acta Chem. Scand.* **20**, 258 (1966).

<sup>420</sup> M. S. Bale, A. B. Simmonds, and W. F. Frager, *J. Chem. Soc., B, Phys. Org.*, 867 (1966).

<sup>421</sup> M. Kumagai, *Nippon Kagaku Zasshi* **81**, 492 (1960); *Chem. Abstr.* **55**, 6477 (1961).

with benzaldehyde or chloral<sup>161, 246, 277, 422</sup> and phthalic anhydride<sup>161</sup> are known. Likewise, 3,6-dimethylpyridazine gives the bis-styryl derivative with benzaldehyde and related products with other aromatic or heterocyclic aldehydes.<sup>423</sup> Claisen condensation of 3- or 4-methylpyridazine with diethyloxalate has been used for the preparation of ethyl 3-(or 4-)pyridazinylpyruvate, intermediate in the synthesis of 3-(and 4-)pyridazinylalanine.<sup>424</sup>

### B. HALOPYRIDAZINES

Halogenated pyridazines play an important part in pyridazine research, since by nucleophilic displacement of the halogen(s) numerous otherwise relatively inaccessible pyridazines become available. There are two main methods of introducing a halogen into the pyridazine nucleus. Several halopyridazines have been prepared by cyclization of open-chain compounds (Section III), in particular 4- and/or 5-halopyridazines; by contrast, 3- and/or 6-halopyridazines are made almost exclusively from the corresponding pyridazinones. Here, the  $\text{—NH—CO—}$  group is transformed with excess of a halogenating agent such as  $\text{POCl}_3$ ,  $\text{PCl}_5$ , or  $\text{PBr}_5$  into the  $\text{—N=CX—}$  group. In few cases this method has been used for 4-halo compounds.<sup>351, 388</sup>

By one or other of these methods 3-chloro-<sup>12, 13, 115, 314, 425, 426</sup> 3-bromo-<sup>115</sup> 3,6-dichloro-<sup>23, 311, 315, 427, 428</sup> 3,6-dibromo-<sup>428, 429</sup> 3,4,5-trichloro-<sup>313</sup> 3,4,6-trichloro-<sup>277, 428, 430</sup> 3,4,5,6-tetrachloro-<sup>428</sup> 3-

<sup>422</sup> R. G. Jones, E. C. Kornfeld, and K. C. McLaughlin, *J. Am. Chem. Soc.* **72**, 3539 (1950).

<sup>423</sup> R. N. Castle and K. Kaji, *J. Heterocyclic Chem.* **2**, 463 (1965).

<sup>424</sup> W. J. Haggerty, R. H. Springer, and C. C. Cheng, *J. Heterocyclic Chem.* **2**, 1 (1965).

<sup>425</sup> G. Favini and M. Simonetta, *Gazz. Chim. Ital.* **89**, 2222 (1959).

<sup>426</sup> R. F. Homer, H. Gregory, W. G. Overend, and L. F. Wiggins, *J. Chem. Soc.*, 2195 (1948).

<sup>427</sup> Z. Brzozowski, A. Jackiewicz, F. Muzalewski, T. Stefanski, and T. Szczepkowska, *Acta Polon. Pharm.* **17**, 355 (1960).

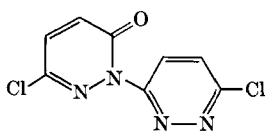
<sup>428</sup> P. Coad, R. A. Coad, S. Clough, J. Hyepock, R. Salisbury, and C. Wilkins, *J. Org. Chem.* **28**, 218 (1963).

<sup>429</sup> J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta* **37**, 121 (1954).

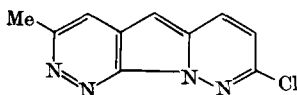
<sup>430</sup> V. G. Nyrkova, T. V. Gortinskaya, and M. N. Shchukina, *Zh. Organ. Khim.* **1**, 1688 (1965).



chloro-4-methyl-,<sup>431</sup> 3-chloro-5-methyl-,<sup>268, 431</sup> 3-chloro-6-methyl-,<sup>117, 161, 401, 432</sup> 3-bromo-6-methyl-,<sup>115</sup> 3-chloro-4,6-alkyl or aryl-,<sup>116, 139, 149, 160</sup> 3-chloro-5,6-dimethyl- or diphenyl-,<sup>126, 139, 268</sup> 3-chloro-6-carboxy- or carbalkoxy-,<sup>426, 433</sup> 4-chloro-3,6-dimethyl-,<sup>351</sup> 3,6-dichloro-(or dibromo-)4-methyl-,<sup>277, 294, 296, 428, 429</sup> 3,6-dichloro-4-phenyl-,<sup>116</sup> 3,6-dichloro-4,5-alkyl- and aryl-,<sup>116, 126, 360</sup> 3-chloro-6-arylpyridazines<sup>11, 154, 164, 169</sup> and other more complex halopyridazines have been prepared.



(66)



(67)

A detailed investigation of the preparation of 3,6-dichloropyridazine from maleic hydrazide and  $\text{POCl}_3$  showed that the product can be contaminated by two other components, 6-chloro-3(2H)-pyridazinone and **66**.<sup>311, 428, 429</sup> The former, as the attacking nucleophile, is responsible for the formation of **66**. Likewise, reaction conditions have been found of importance when preparing 3-chloro-4-methylpyridazine and here structure **67** has been proposed for the by-product.<sup>432</sup>

Since pyridazines are known to undergo electrophilic substitution only with difficulty, direct halogenation is not expected to be a method of wide application. Therefore, bromine in acetic acid is widely used for dehydrogenation of reduced pyridazines. In some instances simultaneous dehydrogenation of the pyridazine nucleus and bromination of the attached aryl radical has been observed.<sup>11, 161, 184, 434</sup> Dehydrogenation and replacement of hydroxyls with bromine atoms occurs if hexahydro-3,6-pyridazinedione is treated with excess  $\text{POBr}_3$ , giving 3,6-dibromopyridazine.<sup>435</sup>

<sup>431</sup> N. Takahayashi, *Pharm. Bull. (Tokyo)* **5**, 229 (1957).

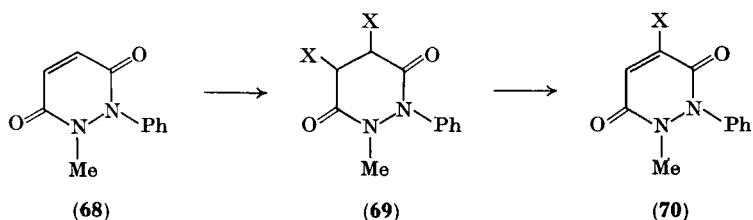
<sup>432</sup> N. K. Basu and F. L. Rose, *J. Chem. Soc.*, 5560 (1963).

<sup>433</sup> S. Mitsui and H. Saito, *Nippon Kagaku Zasshi* **78**, 577 (1957); *Chem. Abstr.* **53**, 5275 (1959).

<sup>434</sup> W. G. Overend, L. M. Turton, and L. F. Wiggins, *J. Chem. Soc.*, 3505 (1950).

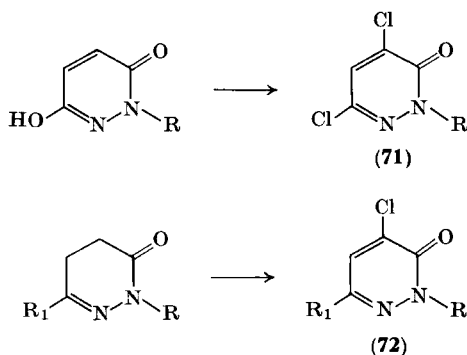
<sup>435</sup> C. Pedrali and A. Mantegani, *J. Org. Chem.* **23**, 778 (1958).

Nevertheless, direct chlorinations are also known. 3,6-Dichloro-pyridazine can be converted by means of  $\text{PCl}_5$  into 3,4,5,6-tetrachloropyridazine.<sup>436</sup> In 5,6-(or 4,6-)dichloro-2-phenyl-3(2*H*)-pyridazinone chlorine enters position 4 or 5,<sup>437</sup> and chlorination of molten 2,6-dimethyl-3(2*H*)-pyridazinone gives four substances, two of which were identified as its 5-chloro- and 4,5-dichloro derivatives.<sup>314</sup> 1-Methyl-2-phenyl-3,6-pyridazinedione (**68**) adds bromine or chlorine



to give the 4,5-dihalo adduct (**69**,  $\text{X} = \text{Br}, \text{Cl}$ ) which is stable in neutral media, but dehydrohalogenation occurs in the presence of base to give solely the 4-halogenated product (**70**,  $\text{X} = \text{Cl}$  or  $\text{Br}$ ).<sup>288</sup> The 1,2-dimethyl analog adds bromine similarly.<sup>289</sup>

Simultaneous introduction of chlorine and dehydrogenation or substitution of the potential hydroxyl with chlorine has been performed with several 3(2*H*)-pyridazinones using a mixture of  $\text{POCl}_3$  and  $\text{PCl}_5$ . The chlorine atom enters always at position 4 (**71** and **72**).<sup>107, 159, 193, 194, 272</sup>



<sup>436</sup> R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *Chem. & Ind. (London)*, 904 (1966).

<sup>437</sup> Y. Maki and K. Obata, *Yakugaku Zasshi* **83**, 819 (1963); *Chem. Abstr.* **60**, 1742 (1964).

Introduction of chlorine into the pyridazine nucleus is possible also via pyridazine *N*-oxides (Section IV, G). Hypohalous acids react with pyridazinones with unsubstituted NH groups to yield the relatively stable *N*-halopyridazinones,<sup>3</sup> and it is also possible to replace the hydrazino group of a hydrazinopyridazine with bromine atom with a mixture of hypobromous and hydrobromic acids.<sup>438</sup>

The only fluoro- and the few iodopyridazines known were all prepared by halogen exchange reactions. Perfluoropyridazine is available from tetrachloropyridazine and KF at 340°, but it polymerizes rapidly at its b.p.<sup>436</sup> Iodopyridazines have been prepared from the corresponding chloro or bromo analogs with boiling hydriodic acid, a reagent much used formerly with or without red phosphorus for dehalogenation of halopyridazines.<sup>11, 126, 154, 161, 294, 428</sup> Formation of iodopyridazines is particularly favored when fresh HI is used. A mixture of acetone and HI can be applied to bromo- but not to chloropyridazines.<sup>428</sup> A superior method was introduced by Coad *et al.*<sup>428</sup>; here halopyridazines are treated with NaI in acetone solution in the presence of a catalytic amount of hydriodic acid. Some iodopyridazines are not particularly stable and readily liberate iodine on standing in solution.

The reactivity of halogen(s) attached to the pyridazine nucleus towards nucleophilic attack is greatly influenced by the kind and position of the halogen, the nucleophile, influence of other groups present, reaction conditions, etc. Interrelations of reactivity of azine positions toward nucleophiles has been compiled in Volume 4 of this series, Chapter VI, Section III, A, 1.

In comparison with 2-chloropyridine which is quite stable, 3-chloropyridazine decomposes easily even when kept at 0°. <sup>426</sup> This instability may be due to self-quaternization, since replacement of the chlorine by other groups requires relatively high temperatures.

Since kinetic data are scarce, a comparison of relative reactivities of halogen atoms at different positions in the pyridazine or pyridazinone ring is difficult. The differences in reactivities which will be referred to are based on synthetic work.

A study of the displacement of the chlorine by methoxide in a series of 6-substituted 3-chloropyridazines revealed that in most cases the reaction followed bimolecular kinetics and thermodynamic

<sup>438</sup> F. Yoneda, T. Ohtaka, and Y. Nitta, *Chem. Pharm. Bull. (Tokyo)* **14**, 698 (1966).

parameters have been found to be similar to those in other hetero-aromatic systems.<sup>439</sup> Furthermore, electron-withdrawing substituents at position 6 facilitate the above-mentioned replacement.

Although it is known that a chlorine atom at the 4-(or 5-)position is more reactive than at the 3- or 6-position for nucleophilic substitution, 3-acetamido-(or amino-)5-chloro-6-methoxypyridazine is resistant to hot aqueous sodium hydroxide and 30% sodium hydrogen sulfide solution, but susceptible to solvolysis in acetic acid containing anhydrous potassium acetate to yield the 5-hydroxy derivative.<sup>440</sup>

As a result of activation by the additional halogen, 3,6-dihalopyridazines and related polyhalopyridazines are more reactive. One chlorine in 3,6-dichloropyridazine is displaced much more easily than the second by nucleophiles. This is due to the incoming group which usually exerts an electron-releasing effect and thus counteracts the electron-withdrawing effect (activating) of the pyridazine nitrogen atoms. For example, 3,6-dichloropyridazine is converted in 15 minutes with hot 2 *N* sodium hydroxide into 6-chloro-3(2*H*)-pyridazinone, but the second chlorine atom remains bound after several hours' reflux.<sup>429, 441</sup> Similar differences in reactivity are reported for the reactions with other nucleophiles. Bromine, attached to the 3- and/or 6-position of the pyridazine ring, is more reactive than chlorine as is usually observed in other cases of nucleophilic substitution. Deactivating effects in 3-halopyridazines bearing various substituents at position 6 (and others) have been discussed in Volume 4, Chapter VI. The replacement of one or both chlorines of 3,6-dichloropyridazine with various nucleophiles to give pyridazines with different functional groups is dealt with in the following sections. The high reactivity of 3,6-dichloropyridazine is shown also by its electrophilic reactivity under the conditions of the Friedel-Crafts reaction. Thus, resorcinol and quinol have been substituted with the chloropyridazinyl residue at positions 4 and 2, respectively.<sup>441a</sup> 3,6-Dichloropyridazine reacts with *n*-butyllithium at  $-15^{\circ}$  to form 6-chloro-3-pyridazinyl lithium.<sup>442</sup>

In 3,4,5- or 3,4,6-trichloropyridazine, the chlorine atom at position 4 is usually the most reactive for nucleophilic attack. Theoretical

<sup>439</sup> J. H. M. Hill and J. G. Krause, *J. Org. Chem.* **29**, 1642 (1964).

<sup>440</sup> T. Horie, *Chem. Pharm. Bull. (Tokyo)* **11**, 1157 (1963).

<sup>441</sup> S. Du Brouil, *J. Org. Chem.* **26**, 3382 (1961).

<sup>441a</sup> A. Pollak, B. Stanovnik, and M. Tišler, *J. Org. Chem.* **31**, 4297 (1966).

<sup>442</sup> G. Rosscools, *Bull. Soc. Chim. Belges* **75**, 5 (1966).

calculations made by means of the LCAO-MO method for 3,4,6-trichloropyridazine<sup>438</sup> are in full accordance with the experimental findings. The lowest electron density is found at the 4-position and the superdelocalizability for nucleophilic attack is greatest at this position. Experimental results are consistent with this and 3,4,6-trichloropyridazine undergoes 4-substitution with alkoxides,<sup>443, 444</sup> hydrazine,<sup>443</sup> sulfonamides,<sup>445, 446</sup> ammonia or amines,<sup>430, 438, 446-449</sup> hydroxide,<sup>444</sup> phenols,<sup>450</sup> or thiophenols.<sup>438, 451</sup> However, in an attempt to prepare 4-hydroxy-3,6-dichloropyridazine, 3,4,6-trichloropyridazine as refluxed with acetic acid, afforded only 4,6- or 5,6-dichloro-3(2*H*)-pyridazinone.<sup>443</sup> Similarly, 3,4,5-trichloropyridazine yielded 4,5-dichloro-3(2*H*)-pyridazinone.<sup>443</sup> The preferred displacement of chlorine atoms adjacent to ring nitrogens can be explained in terms of hydrogen-bonded transition states involving ring nitrogens (see Volume 4, Chapter VI, Section II, F), followed by acid-catalyzed substitution.

3,4,5-Trichloropyridazine when heated under pressure with  $\text{NH}_3/\text{EtOH}$  yielded a mixture of aminodichloropyridazines, believed to be the 4- and 5-amino isomers.<sup>313</sup> A modified procedure gave a mixture of 4-amino-3,5-dichloropyridazine (35%) and 5-amino-3,4-dichloropyridazine (38%) and structures of both isomers have been proved through further transformations.<sup>449</sup> With equimolar amount of methoxide the 5-chlorine is displaced, but with 2 equivalents of methoxide 3,4,5-trichloropyridazine yielded a mixture of 4-chloro-3,5-dimethoxy- (25%) and 3-chloro-4,5-dimethoxypyridazine (41%).<sup>451</sup>

<sup>443</sup> T. Kuraishi, *Pharm. Bull. (Tokyo)* **5**, 376 (1957).

<sup>444</sup> K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta* **39**, 1755 (1956).

<sup>445</sup> M. Yanai, T. Kuraishi, and T. Kinoshita, *Yakugaku Zasshi* **81**, 708 (1961).

<sup>446</sup> T. Nakagome, T. Hayama, T. Komatsu, and Y. Eda, *Yakugaku Zasshi* **82**, 1103 (1962).

<sup>447</sup> V. G. Nyrkova, T. V. Gortinskaya, and M. N. Shchukina, *Zh. Obshch. Khim.* **34**, 3132 (1964).

<sup>448</sup> T. Kuraishi, *Pharm. Bull. (Tokyo)* **4**, 137 (1956).

<sup>449</sup> T. Kuraishi and R. N. Castle, *J. Heterocyclic Chem.* **1**, 42 (1964).

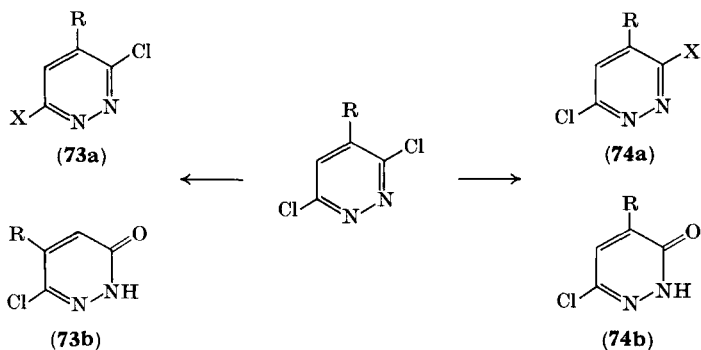
<sup>450</sup> T. Jojima and S. Tamura, *Agr. Biol. Chem. (Tokyo)* **29**, 151 (1965).

<sup>451</sup> F. Yoneda, T. Ohtaka, and Y. Nitta, *Chem. Pharm. Bull. (Tokyo)* **11**, 954 (1963).

<sup>452</sup> T. Itai and S. Kamiya, *Chem. Pharm. Bull. (Tokyo)* **11**, 1059 (1963).

3,4,5,6-Tetrafluoropyridazine reacts easily with aqueous ammonia at 0° and again the fluorine at position 4 is replaced by an amino group.<sup>436</sup>

However, the presence of other groups in the pyridazine nucleus may exert additional influences and a selective exchange or competitive monosubstitution has been observed. In the case of 4-substituted 3,6-dichloropyridazines monosubstitution of the individual chlorine atoms with nucleophiles can give two isomeric compounds, **73a** and **74a**.



Druey *et al.*<sup>429</sup> have performed reactions of 4-methyl-3,6-dichloropyridazine with ammonia and other nucleophiles, but did not establish their structures. Later studies revealed that treatment of the mentioned pyridazine with anhydrous ammonia in methanol at 120° afforded a mixture of aminochloro-4-methylpyridazines in the ratio of about 1:10, the isomer **73a** (X = NH<sub>2</sub>, R = Me) predominating.<sup>296</sup> Also modified reaction conditions have led to a mixture of both isomers,<sup>453</sup> where the isomer **73a** was prevailing,<sup>431</sup> and when dimethylamine has been used only isomer **73a** (R = Me, X = NMe<sub>2</sub>) was isolated.<sup>296, 454</sup> From the reaction with hydrazine hydrate the isomer **74a** (R = Me, X = NHNH<sub>2</sub>) is claimed to be the main product.<sup>431</sup> A reinvestigation of this reaction and structure determination of both isomers presented contrary results. Thus, 3-chloro-6-hydrazino-4-methylpyridazine and 3-chloro-6-hydrazino-5-methylpyridazine were

<sup>453</sup> K. Mori, *Yakugaku Zasshi* **82**, 304 (1962); *Chem. Abstr.* **58**, 3427 (1963).

<sup>454</sup> S. Linholter, R. Rosenoern, and L. Vincents, *Acta Chem. Scand.* **17**, 960 (1963).

formed in the ratio of about 2:1.<sup>455</sup> With other nucleophiles studied, the isomers **74** are formed in greater amount. 3,6-Dichloro-4-methylpyridazine reacts with sodium methoxide to give the 3-methoxy isomer (**74a**, R=Me, X=OMe) as the main<sup>296, 453, 456</sup> or sole<sup>431</sup> product, but with increasing size of the alkoxide alkyl group 6-alkoxylation (**73a**, R=Me, X=OR) is preferred.<sup>296</sup> Hydrolysis with alkali, acetic, or hydrochloric acid favors the displacement of the 3-chlorine and the isomer **74b** prevails over **73b**.<sup>296, 431, 457</sup> From the reaction with KHS the isomer **74a** (R=Me, X=SH) has been isolated.<sup>431</sup>

Selective exchange of chlorine atoms is reported for the related 4-amino- or 4-sulfonamido-3,6-dichloropyridazines when molecular proportions of nucleophiles are used and here the 3-chlorine is replaced by hydrazino or alkoxy groups.<sup>445, 446, 458</sup> This is interpreted as a result of a greater para indirect deactivation (6-chlorine) relative to ortho direct deactivation (chlorine at position 3). Similarly, in the isomeric 5-amino-3,4- and 4-amino-3,5-dichloropyridazine the 3-chlorine is substituted for alkoxy groups.<sup>458</sup> However, if the reaction between 4-amino-3,6-dichloropyridazine and excess of sodium methoxide or potassium hydroxide in methanol at an elevated temperature is performed, a mixture of several products is obtained.<sup>446, 459</sup> The main products are 4-amino-3,6-dimethoxypyridazine (40–45%) and 4-amino-6-chloro-3(2*H*)-pyridazinone (21–30%) which result from the intermediate 4-amino-6-chloro-3-methoxypyridazine by replacement of chlorine or demethylation of the methoxy group. A third compound, isolated in low yield (3%) was identified as 4-amino-6-methoxy-3(2*H*)-pyridazinone.

The most reactive halogen of halo-3(2*H*)-pyridazinones is that at position 5. Considering the group  $\text{—CO—C=C—Cl}$ , these halo-pyridazinones can be regarded as cyclic vinylogs of acid chlorides. With a variety of nucleophiles 4,5-dihalo-3(2*H*)-pyridazinones react with the halogen on position 5, which can be exchanged in the reaction with alkoxides,<sup>275, 306, 423, 437</sup> hydroxide,<sup>286, 297</sup> ammonia or amines,<sup>3</sup>

<sup>455</sup> S. Linholter and R. Rosenoern, *Acta Chem. Scand.* **16**, 2389 (1962).

<sup>456</sup> T. Nakagome, *Yakugaku Zasshi* **82**, 1005 (1962).

<sup>457</sup> T. Kuraishi, *Pharm. Bull. (Tokyo)* **5**, 587 (1957).

<sup>458</sup> M. Yanai and T. Kinoshita, *Yakugaku Zasshi* **82**, 857 (1962).

<sup>459</sup> T. Nakagome, A. Kobayashi, A. Misaki, T. Komatsu, T. Mori, and S. Nakanishi, *Chem. Pharm. Bull. (Tokyo)* **14**, 1065 (1966).

275, 286, 299, 306, 319, 423, 460–462 hydrazine,<sup>461, 463, 464</sup> hydrosulfide, or thiophenates,<sup>286, 465</sup> and similar reaction takes place between 5,6-dihalo-3(2*H*)-pyridazinone and amines or ammonia.<sup>275, 286, 299, 319</sup> However, it has recently been found<sup>299</sup> that 4,5-dichloro-2,6-dimethyl-3(2*H*)-pyridazinone when heated with aqueous ammonia at 140–150° for 10 hours gave a mixture of 4-amino-5-chloro-2,6-dimethyl-3(2*H*)-pyridazinone (42%) and 5-amino-4-chloro-2,6-dimethyl-3(2*H*)-pyridazinone (47%).

4,6-Dihalo-3(2*H*)-pyridazinones possess a reactive 4-halogen and chlorine is displaced easily at room temperature with dimethylamine or with hydroxide or ammonia upon heating,<sup>299, 466</sup> but the introduction of a second dimethylamino group required heating at 170–180° for 60 hours.<sup>272</sup> Under similar vigorous reaction conditions (150–160°, 10 hours) the dimethoxy analog is formed.<sup>467</sup> Likewise, 2-phenyl-4,5,6-trichloro-3(2*H*)-pyridazinone is transformed into 4,6-dichloro-5-hydroxy-2-phenyl-3(2*H*)-pyridazinone when heated with methanolic sodium hydroxide, but treatment with methoxide gives, besides the 4,6-dichloro-5-methoxy derivative, 6-chloro-4,5-dimethoxy and 4,5,6-trimethoxy derivatives,<sup>466</sup> again showing that reactivity of chlorine in this trichloropyridazinone is greatest at the 5-position and least at the 6-position. A discussion of different effects and their influences on the relative ease of halogen displacement in pyridazinones is given in Volume 4, Chapter VI, Section II, E, 2.

With SH<sup>−</sup>, P<sub>4</sub>S<sub>10</sub>, and thiols, displacement of halogens in polyhalopyridazines and pyridazones proceeds usually at elevated temperatures with all halogens present in the nucleus.

Reactive chlorine atoms at the 4-position may also be replaced by nitro groups using sodium nitrite in dimethylformamide. Thus, 4,5-dichloro-3(2*H*)-pyridazinones have been converted into 4-hydroxy-5-nitro-3(2*H*)-pyridazinones, the replacement of the second chlorine by a hydroxyl taking place simultaneously.<sup>3</sup>

<sup>460</sup> R. N. Castle and W. S. Seese, *J. Org. Chem.* **23**, 1534 (1958).

<sup>461</sup> J. Bourdais, *Bull. Soc. Chim. France*, 2124 (1964).

<sup>462</sup> A. Pollak and M. Tišler, *Tetrahedron* **21**, 1323 (1965).

<sup>463</sup> W. M. Osner, R. N. Castle, and D. L. Aldous, *J. Pharm. Sci.* **52**, 539 (1963).

<sup>464</sup> F. Kuhelj, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta* **38**, 299 (1966).

<sup>465</sup> F. Yoneda, T. Ohtaka, and Y. Nitta, *Chem. Pharm. Bull. (Tokyo)* **13**, 580 (1965).

<sup>466</sup> Y. Maki and K. Obata, *Chem. Pharm. Bull. (Tokyo)* **12**, 176 (1964).

<sup>467</sup> J. Druey, K. Meier, and A. Staehelin, *Pharm. Acta Helv.* **38**, 498 (1963).



Evidence that nucleophilic substitution of pyridazines may occur also via the hetaryne mechanism has been presented in the case of 1-methyl-2-phenyl-4-chloro-(or bromo-)-3,6-pyridazinedione<sup>468, 469</sup> which, when treated with piperidine, yielded the 4- and 5-piperidino isomers. Formation of the 5-methoxy isomer as the sole product from the above 4-chloro compound<sup>467</sup> can be interpreted also in terms of an intermediate hetaryne formation.

In addition to the foregoing nucleophilic displacements, some substituted halopyridazines undergo simultaneous cyclization to form polyazaheterocycles. Several of such polycyclic systems have been reviewed.<sup>2, 3</sup>

### C. PYRIDAZINONES AND DERIVATIVES

Pyridazines with "hydroxyl" groups (generally in the oxo form) at different positions in the ring can be prepared by several methods as outlined in Section III. Syntheses from open-chain compounds are particularly suitable for obtaining 3(2*H*)-pyridazinones and their 6-hydroxy analogs. If more complex pyridazinones are available, such as halogenated pyridazinones, catalytic dehalogenation is one of the preferred methods. In this manner 3(2*H*)-pyridazinone<sup>115, 315, 444</sup> and its 2-phenyl,<sup>272</sup> 4- and 5-methyl,<sup>431, 453</sup> 2-phenyl-4-(and 5-)-methyl,<sup>272</sup> and 3,4-diphenyl<sup>168</sup> analogs, 4(1*H*)-pyridazinone, and 1-methyl-4(1*H*)-pyridazinone<sup>443, 444</sup> were prepared.

Another possibility is the decarboxylation of 3(2*H*)-pyridazinone-carboxylic acids and this has been used in the preparation of 3(2*H*)-pyridazinone itself,<sup>12, 13, 267, 314, 425, 426</sup> its 3-, 4-, or 5-methyl<sup>268, 470</sup> 3,4-dimethyl,<sup>268</sup> or 3,4-diphenyl<sup>267</sup> analogs, and 4(1*H*)-pyridazinone.<sup>351</sup>

Several 3(2*H*)-pyridazinones are made from 3-chloropyridazines, such as 6-methyl-3(2*H*)-pyridazinone,<sup>426</sup> and the 6-chloro<sup>443, 471</sup> or 4-amino analog,<sup>319</sup> or from the corresponding alkoxy compounds on acid or basic hydrolysis. 6-Chloro-3(2*H*)-pyridazinone is best prepared

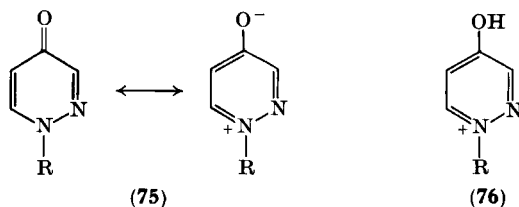
<sup>468</sup> T. Kauffmann and A. Risberg, *Tetrahedron Letters*, 1459 (1963).

<sup>469</sup> T. Kauffmann, A. Risberg, J. Schulz, and R. Weber, *Tetrahedron Letters*, 3563 (1964).

<sup>470</sup> F. H. McMillan, K. A. Kun, C. B. McMillan, B. S. Schwartz, and J. A. King, *J. Am. Chem. Soc.* **78**, 407 (1956).

<sup>471</sup> E. A. Steck and R. P. Brundage, *J. Am. Chem. Soc.* **81**, 6511 (1959).

from 3,6-dichloropyridazine but it has also been obtained from 3-chloro-6-methoxypyridazine by using  $\text{NH}_3/\text{MeOH}$  ( $150\text{--}170^\circ$ , 24 hours).<sup>472</sup> Thus, hydrochloric acid has been used for the synthesis of 4- or 5-methyl-3(2*H*)-pyridazinone,<sup>296</sup> and dilute sodium hydroxide for obtaining 6-chloro-4-(or 5-)methyl-3(2*H*)-pyridazinone.<sup>456</sup> 4(1*H*)-Pyridazinone has been prepared from 4-ethoxypyridazine using  $\text{HBr}$  in glacial acetic acid for displacement of the alkoxy group.<sup>443</sup>



Like other azines with a hydroxyl group  $\alpha$  or  $\gamma$  to a ring nitrogen atom, 3- and 4-hydroxypyridazines exist predominantly in the oxo form in the solid state and in aqueous solution. This has been established for 3(2*H*)-pyridazinone and related compounds from correlations of ultraviolet spectra of unsubstituted compounds and their *O*- and *N*-methyl derivatives in neutral, acid, and alkaline solution, on the basis of infrared spectra (for a summary of this aspect of tautomerism see Volume 1, Chapter VII, Section II, K) and from the determined crystal structure of 6-oxo-1,6-dihydro-3-pyridazine-carboxamide.<sup>31, 32</sup> Here, the bond lengths and positions of hydrogen atoms clearly indicate its structure as the oxo form. Similar conclusions were reached also for 4(1*H*)-pyridazinones (75) and the predominant cationic structure is represented by 76.<sup>444, 473, 474</sup>

Tautomeric equilibria for pyridazines with potential hydroxyl functions have been measured and the determined  $K_T$  values are smaller compared with those of the corresponding pyridines.<sup>473</sup> Furthermore, it is concluded that tautomerization to zwitterionic forms is repressed when solvents of low dielectric constants are used. On this basis, pyridazinones are expected to possess aromatic

<sup>472</sup> T. Horie, K. Kinjo, and T. Ueda, *Chem. Pharm. Bull. (Tokyo)* **10**, 580 (1962).

<sup>473</sup> S. F. Mason, *J. Chem. Soc.*, 5010 (1957).

<sup>474</sup> A. Staehelin, K. Eichenberger, and J. Druey, *Helv. Chim. Acta* **39**, 1741 (1956).

properties, and this is supported by spectroscopic and chemical evidence.

Maleic hydrazide has also been investigated in detail and its structure determined as the monohydroxymonooxo form,<sup>475</sup> i.e., 6-hydroxy-3(2*H*)-pyridazinone, from spectroscopic data (for summary see Volume 1 of this Series, Chapter VII, p. 366). Similar conclusions were reached for substituted maleic hydrazides, although for 4- or 5-substituted maleic hydrazides it is not known which of the amide groups relative to the substituent is in the lactam and which in the enolized form.

NMR investigations on maleic hydrazide have been made and the dioxo form was first proposed.<sup>476</sup> Later it has been shown that chemical shift evidence is strongly in favour of the monohydroxy form.<sup>477, 478</sup> On the basis of spectroscopic data it is also concluded that in the crystalline state the molecules of maleic hydrazide are connected by very strong hydrogen bonds and are strongly polarized.<sup>479-481</sup> This interaction is usually retained in weakly polar solvents. An indication of association has been reached also for 6-methyl-3(2*H*)-pyridazinone on the basis of molecular weight determinations in benzene solution.<sup>402</sup>

p*K* values of some pyridazinones are presented in Table II. The ring nitrogen unsubstituted 3(2*H*)-pyridazinones are weak acids, they all form salts with strong bases, and some of them even with ammonia and amines. The same observations as for monoazines are valid for pyridazinones; i.e., the p*K<sub>a</sub>* value of an unmethylated cyclic amide is considerably lower than that of the *O*-methylated product and equal to or somewhat higher than that of its *N*-methyl derivative.<sup>417</sup> Maleic hydrazide is more acidic than pyridazine mono-ones, and compounds of this type form monometallic salts with base; unstable dimetallic salts are prepared only with difficulty, or not at all.<sup>284</sup>

<sup>475</sup> F. Arndt, *Rev. Fac. Sci. Univ. Istanbul*, **9A**, 19 (1944).

<sup>476</sup> R. Gompper and P. Altreuther, *Z. Anal. Chem.* **170**, 205 (1959).

<sup>477</sup> A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1523 (1964).

<sup>478</sup> O. Ohashi, M. Mashina, and M. Kubo, *Can. J. Chem.* **42**, 970 (1964).

<sup>479</sup> Yu. N. Sheinker, T. V. Gortinskaya, and T. P. Sycheva, *J. Chim. Phys.* **55**, 217 (1958).

<sup>480</sup> Yu. N. Sheinker, T. V. Gortinskaya, and T. P. Sycheva, *Zh. Fiz. Khim.* **31**, 599 (1957).

<sup>481</sup> Yu. N. Sheinker and Yu. I. Pomerantsev, *Zh. Fiz. Khim.* **30**, 79 (1956).

Dielectric constants<sup>47, 482</sup> and polarography<sup>483-487</sup> of pyridazinones and maleic hydrazide are recorded.

Maleic hydrazide was first prepared by Curtius and Foersterling in 1895<sup>270</sup> and in 1949 it was introduced as a "growth regulator."<sup>488</sup> A literature summary on maleic hydrazide<sup>489</sup> and reviews of its herbicidal properties have appeared.<sup>490, 491</sup>

TABLE II  
pK<sub>a</sub> VALUES

Compound	Proton gain	Proton loss
3(2 <i>H</i> )-Pyridazinone <sup>a</sup>	-1.8	10.46
4(1 <i>H</i> )-Pyridazinone <sup>a</sup>	1.07	8.68
3-Methoxypyridazine <sup>a</sup>	2.52	—
4-Methoxypyridazine <sup>a</sup>	3.70	—
2-Methyl-3(2 <i>H</i> )-pyridazinone <sup>b</sup>	-2.1	—
1-Methyl-4(1 <i>H</i> )-pyridazinone <sup>b, c</sup>	1.02	—
	1.1	—
6-Hydroxy-3(2 <i>H</i> )-pyridazinone <sup>a, d, e</sup>	5.5	13
	5.65	—
	5.67	—
3,6-Dimethoxypyridazine <sup>a</sup>	1.61	—

<sup>a</sup> A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).

<sup>b</sup> A. Albert and G. B. Barlin, *J. Chem. Soc.*, 3129 (1962).

<sup>c</sup> K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta* **39**, 1755 (1956).

<sup>d</sup> H. Feuer and H. Rubinstein, *J. Am. Chem. Soc.* **80**, 5873 (1958).

<sup>e</sup> D. M. Miller, *Can. J. Chem.* **33**, 1806 (1955).

<sup>482</sup> W. Hückel and W. Jahnentz, *Chem. Ber.* **74B**, 652 (1941).

<sup>483</sup> D. M. Miller, *Can. J. Chem.* **33**, 1806 (1955).

<sup>484</sup> D. M. Miller, *Can. J. Chem.* **34**, 1760 (1956).

<sup>485</sup> T. Takeuchi, N. Yokouchi, and K. Onoda, *J. Electrochem. Soc. Japan* **23**, 541 (1955).

<sup>486</sup> T. Takeuchi, N. Yokouchi, and K. Onoda, *Bunseki Kagaku* **5**, 399 (1956); *Chem. Abstr.* **51**, 13652 (1957).

<sup>487</sup> P. Pfügel, G. Wagner, and O. Manousek, *Z. Chem.* **6**, 263 (1966).

<sup>488</sup> D. L. Schoene and O. L. Hoffmann, *Science* **109**, 588 (1949).

<sup>489</sup> United States Rubber, Naugatuck Chemical Division, "A Literature Summary on Maleic Hydrazide." 1949-1957, and 1957-1963.

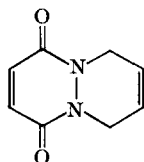
<sup>490</sup> H. D. Tate, *Farm. Chem.* **118**, No. 1, 47 (1955).

<sup>491</sup> E. R. Weber, *Chem. Prod.* **18**, 179 (1955).

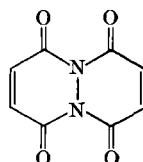
Maleic hydrazide and its 4,5-difluoro analog have been oxidized at low temperatures ( $-50$  to  $-70^\circ$ ) with *tert*-butyl hypochlorite to the unstable cyclic diacyldiimides (**77**,  $R = H$  or  $F$ ).<sup>493, 494</sup> Oxidation with lead tetraacetate proceeds similarly and evidence for the formation of **77** ( $R = H$ ) in this reaction has been presented from the formation of **78**, if the reaction is conducted in the presence of butadiene.<sup>495</sup> These cyclic diacyldiimides decompose rapidly near  $-20^\circ$  and, upon warming the solution of **77** ( $R = H$ ), **79** is obtained as the main product. The



(77)



(78)



(79)

most remarkable characteristic of these diimides is their instant reaction with dienes at  $-77^\circ$ ; they are some of the most reactive dienophiles known.

Pyridazinones have been reported to undergo a number of reactions with substitution on oxygen or nitrogen of the amide group. They can react as "ambident anions"<sup>496</sup> in alkylations, but in view of the complexity of some such reactions this theory seems not to be so simply explainable when applied to pyridazinones.

Alkylations of pyridazinones have been performed in the usual way; i.e., they were treated with an alkylhalide or dialkylsulfate in the presence of a base. Most frequently methylations were performed, but other alkylating agents such as  $\alpha$ -haloacids (or esters),<sup>159, 470, 497-499</sup> alkylaminoalkylhalides,<sup>159, 500, 501</sup> or even 2-bromopyridine<sup>159</sup>

<sup>492</sup> A. Albert and G. B. Barlin, *J. Chem. Soc.*, 3129 (1962).

<sup>493</sup> T. J. Kealy, *J. Am. Chem. Soc.* **84**, 966 (1962).

<sup>494</sup> E. Hedaya, R. L. Hinman, and S. Theodoropoulos, *J. Org. Chem.* **31**, 1311 (1966).

<sup>495</sup> R. A. Clement, *J. Org. Chem.* **27**, 1115 (1962).

<sup>496</sup> N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.* **77**, 6269 (1955).

<sup>497</sup> N. Takahayashi and H. Ronda, *Chem. Pharm. Bull. (Tokyo)* **6**, 722 (1958).

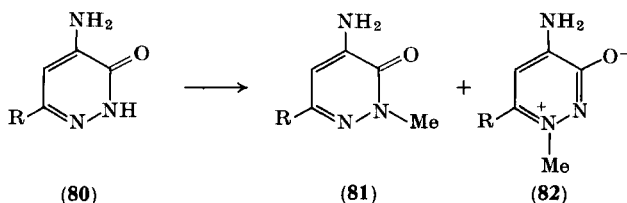
<sup>498</sup> G. Rosseels, *Bull. Soc. Chim. Belges* **73**, 532 (1964).

<sup>499</sup> J. A. King and F. H. McMillan, *J. Am. Chem. Soc.* **74**, 3222 (1952).

<sup>500</sup> A. Lespagnol and J. Deprey, *Bull. Soc. Chim. France*, 606 (1961).

<sup>501</sup> A. Lespagnol and J. Deprey, *Bull. Soc. Chim. France*, 1117 (1962).

were employed. *N*-Alkylated products are invariably obtained. Methylation of 3(2*H*)-pyridazinone with dimethyl sulfate has been claimed superior to methyl iodide.<sup>502</sup> Diazomethane, although known to effect *N*-methylation also,<sup>497</sup> reacted with 6-methyl-3(2*H*)-pyridazinone to give the *O*-methyl derivative in low yield.<sup>402</sup> Benzyla- tion did not give uniform results and a mixture of the *N*- and *O*-benzyl derivatives in the ratio of about 2 : 1 is reported.<sup>503</sup> Likewise, a mixture of the *O*- and *N*-carbethoxymethyl derivatives in the ratio of 10:1



resulted from the reaction between 6-chloro-3(2*H*)-pyridazinone and diazoacetic ester.<sup>498, 504</sup> Methylation of 6-substituted 4-amino-3(2*H*)-pyridazinones (80, R = H, Me, Cl, OMe) with dimethylsulfate below 10° gave varying yields of the 2-methyl derivatives (81) and betaines (82), depending on the size of the substituent at the 6-position.<sup>504a</sup> If position 6 is unsubstituted, the yield of both types of compound is the same, but 6-substituted pyridazinones gave the 2-methyl derivatives (81, R = Me, Cl, OMe) in about 80% yield.

As expected, maleic hydrazide is alkylated to give various mono- or dialkylated products and many investigations have been devoted to this problem. Methylation with diazomethane was investigated formerly in connection with the structure of maleic hydrazide. The mono-*O*-methyl derivative was formed first and further methylation afforded the *N,O*-dimethyl compound (85).<sup>284, 505</sup>

Methylation of maleic hydrazide with dimethyl sulfate can give, depending on reaction conditions, three different methylated products.<sup>289, 291</sup> In the presence of aqueous base the 2-methyl derivative (83) is obtained, whereas heating with dimethyl sulfate at

<sup>502</sup> S. Hünig and K.-H. Oette, *Ann. Chem.* **640**, 98 (1961).

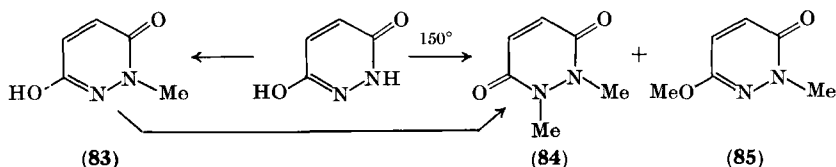
<sup>503</sup> D. L. Aldous and R. N. Castle, *Arzneimittel-Forsch.* **13**, 878 (1963).

<sup>504</sup> G. Rosseels, G. Thuillier, and P. Rumpf, *Compt. Rend.* **254**, 1450 (1962).

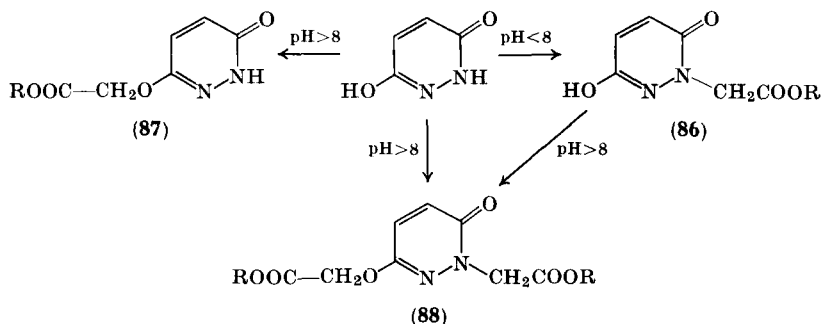
<sup>504a</sup> T. Nakagome, A. Misaki, and A. Murano, *Chem. Pharm. Bull. (Tokyo)* **14**, 1090 (1966).

<sup>505</sup> F. Arndt, *Angew. Chem.* **61**, 397 (1949).

150° afforded a mixture of the 1,2-dimethyl (**84**) and 2-methyl-6-methoxy (**85**) derivatives in almost equal amounts. Prolonged heating favors the formation of more **84**. Although **84** and **85** are obtained



also from **83** in about equal amounts with dimethyl sulfate, *N*-substituted analogs of maleic hydrazide are usually *O*-alkylated. One reported *N*-alkylation<sup>506</sup> was later shown to be incorrect.<sup>291</sup> However, a reverse sequence of alkylation has been established if benzyl chloride and analogs are used. Maleic hydrazide affords first the *O*-alkylated product and the second group enters the ring to give the *N,O*-dialkylated product.<sup>507, 508</sup>



The course of alkylation may be influenced by the pH of the reaction medium as shown in the case of chloroacetic acid or its ester as alkylating agent. Maleic hydrazide *N*-alkylates at pH < 8 to form **86**, but at pH > 8 *O*-alkylation (**87**) or *N,O*-dialkylation (**88**) with two equivalents of the alkylating agent can take place.<sup>509</sup> Compound **88** may be formed from **86** indirectly. 6-Chloro-3(2*H*)-pyridazinone

<sup>506</sup> D. Biquard and P. Grammaticakis, *Bull. Soc. Chim. France* [5] **9**, 675 (1942).

<sup>507</sup> Y. Nitta and F. Yoneda, *Chem. Pharm. Bull. (Tokyo)* **11**, 737 (1963).

<sup>508</sup> F. Yoneda and Y. Nitta, *Chem. Pharm. Bull. (Tokyo)* **11**, 669 (1963).

<sup>509</sup> R. Schönbeck, *Monatsh. Chem.* **90**, 284 (1959).

behaves likewise in the reaction with chloroacetic acid to give the *N*-substituted product.<sup>498, 504, 509</sup> The related *O*-substituted derivatives are prepared from 3,6-dichloropyridazine with an alkaline solution of glycollic acid.<sup>498, 509</sup> Failure of the Meerwein reaction in an attempt to arylate maleic hydrazide is reported.<sup>510</sup>

Alkoxy- or aryloxy-pyridazines and the corresponding diethers are usually made from a halo- or dihalopyridazine and an equivalent amount of sodium alkoxide or phenoxide. As by-products 6-alkoxy-3(2*H*)-pyridazinones may be formed (particularly if aqueous bases are used) or other products may result from alkoxide exchange. A detailed examination of the reaction between 3,6-dichloropyridazine and various alkoxides revealed that the crude products, i.e., 3-alkoxy-6-chloropyridazines, are always contaminated with the starting material and the 3,6-bisalkoxy derivative.<sup>511</sup> Lower temperatures and prolonged heating favor the preparation of 3-alkoxy-6-chloropyridazines and similar optimum reaction conditions for the synthesis of 3,6-dialkoxy-<sup>511, 512</sup> and phenoxy-pyridazines<sup>513</sup> are reported.

*O*→*N* rearrangements are known for many 3,6-dialkoxy-pyridazines. 3,6-Dimethoxy-pyridazine when treated with methyl iodide or dimethyl sulfate under relatively mild conditions rearranges to the thermodynamically more stable **85**. At higher temperatures and in the presence of dimethyl sulfate some of **84** is also formed. Isomerizations of this type are known for other alkoxy-pyridazines<sup>291, 467</sup> and azines, for example pyrimidines.<sup>514</sup> The Hilbert-Johnson reaction, which enabled the synthesis of pyrimidine nucleosides, has been applied to the synthesis of maleic hydrazide riboside and 2'-deoxyriboside, starting from 3,6-bisbenzyloxy-pyridazine.<sup>515</sup> Thus it is possible to obtain 2-methyl-6-alkoxy-3(2*H*)-pyridazinones from dialkoxy-pyridazines upon treatment with methyl halides or dimethyl sulfate.<sup>291</sup> A reaction mechanism involving the intermediate quaternization product (**89**) has been suggested.

<sup>510</sup> C. S. Rondestvedt, M. J. Kalm, and O. Vogl, *J. Am. Chem. Soc.* **78**, 6115 (1956).

<sup>511</sup> P. Coad, R. A. Coad, B. Dubinsky, J. P. Buckley, and W. Kinnard, *J. Med. Chem.* **8**, 129 (1965).

<sup>512</sup> E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.* **76**, 4454 (1954).

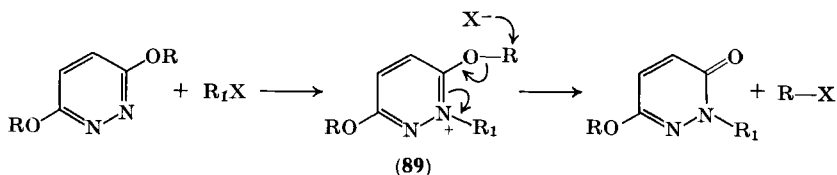
<sup>513</sup> S. Tamura and H. Hojima, *Agr. Biol. Chem. (Tokyo)* **27**, 653 (1963).

<sup>514</sup> G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.* **52**, 2001 (1930).

<sup>515</sup> J. Pliml and F. Šorm, *Collection Czech. Chem. Commun.* **30**, 3744 (1965).

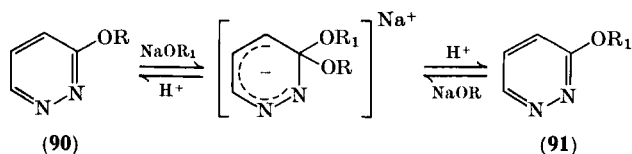


3,6-Dimethoxypyridazine is not rearranged when heated alone to 200° and only prolonged heating at 300° causes some methyl group migration. However, in the presence of strong acids or  $\text{AlCl}_3$  and  $\text{FeCl}_3$  it rearranges quantitatively into **85** at 150°. 3,6-Diethoxypyridazine is isomerized analogously and a reaction mechanism for



these rearrangements has been proposed.<sup>291</sup> 4-Amino-3,6-dimethoxypyridazine is readily transformed into 5-amino-6-methoxy-2-methyl-3(2*H*)-pyridazinone upon heating at 170° for 30 minutes.<sup>299</sup>

Rearrangement of the Claisen type takes place with 3,6-dialloxy-pyridazine at 200° in the presence or absence of a catalyst to give 2-allyl-6-allyloxy-3(2*H*)pyridazinone as the main product along with some 1,2-diallyl-3,6-pyridazinedione.<sup>291</sup>

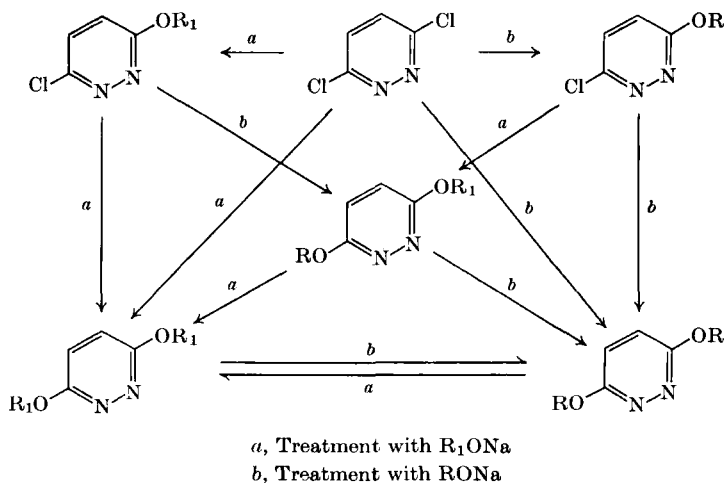


Another interesting feature of alkoxy-pyridazines is their alkoxide exchange. It occurs with 3-alkoxy- and 3,6-dialkoxy-pyridazines and presents additional evidence of the positive nature of the pyridazine ring carbon atoms having attached a more electronegative group than carbon (**90–91**). The results of these studies<sup>516</sup> demonstrate that this type of exchange is general and the possible interchanges are presented in Scheme 1 (R represents an alkyl or a cycloalkyl group and  $\text{R}_1$  a dimethylaminoethyl group).

*O*→*N*-Glycosyl rearrangements of pyridazine glycosides are also known. *O*-β-D-glucosides or ribosides of pyridazinones and maleic

<sup>516</sup> P. Coad, R. A. Coad, and J. Hyepock, *J. Org. Chem.* **29**, 1751 (1964).

hydrazide have been obtained from silver salts of the starting compound and  $\alpha$ -acetobromoglucose or other  $\alpha$ -bromo sugar<sup>517-523</sup> while sodium or potassium salts yielded *N*-2- $\beta$ -D-glucosides.<sup>521, 524</sup> The latter are formed also from the corresponding *O*-glycosides and rearrangement takes place under the influence of mercuric bromide.<sup>517-521, 523, 524a</sup> The *O*-glycosides are also very susceptible to decomposition by acids.



SCHEME 1

Acylation of pyridazinones, maleic hydrazide, and related compounds are known. Either *O*-acylation or *N*-acylation is reported. Using the Schotten-Baumann procedure maleic hydrazide is *O*-acylated with benzoyl chloride and chlorocarbonates<sup>295</sup> and similarly *O*-sulphonyl and phosphoryl derivatives have been prepared.<sup>278, 525</sup>

<sup>517</sup> H. Pischel and G. Wagner, *Z. Chem.* **5**, 227 (1965).

<sup>518</sup> G. Wagner and D. Heller, *Z. Chem.* **5**, 183 (1965).

<sup>519</sup> G. Wagner and D. Heller, *Z. Chem.* **5**, 417 (1965).

<sup>520</sup> G. Wagner and D. Heller, *Arch. Pharm.* **299**, 208 (1966).

<sup>521</sup> G. Wagner and D. Heller, *Naturwissenschaften* **50**, 497 (1963).

<sup>522</sup> G. Wagner and D. Heller, *Pharmazie* **21**, 404 (1966).

<sup>523</sup> G. Wagner and D. Heller, *Arch. Pharm.* **299**, 883 (1966).

<sup>524</sup> G. Wagner and D. Heller, *Z. Chem.* **2**, 306 (1962).

<sup>524a</sup> G. Wagner and D. Heller, *Pharmazie* **21**, 592 (1966).

<sup>525</sup> K. Szabó and E. Oswald, *Acta Chim. Acad. Sci. Hung.* **15**, 1 (1958).

The *N*-acylated derivatives of maleic hydrazide, prepared from open-chain compounds, have been found to differ from acylated products obtained from maleic hydrazide acylations.<sup>278</sup> Acylation of 4- or 5-substituted maleic hydrazides should permit the existence of two *O*-acylated isomers. So far, only one isomer of unknown structure has been isolated from benzoylation of the 4-methyl analog.<sup>295</sup> Maleic hydrazide and its 2-substituted analogs are *O*-acylated with acetic anhydride, acyl halides,<sup>272, 278, 526</sup> and *O,O*-dialkylphosphorochloridothioates<sup>441</sup>; the acyl groups are readily removed by hydrolysis.

A few instances of *N*-acylation are also known. 6-Chloro-3(2*H*)-pyridazinone reacts preferentially on the nitrogen with chlorocarbonates and the structure of the products has been assigned on the basis of IR data.<sup>527</sup> *N*-Acylation of maleic hydrazide are claimed to proceed with unsaturated acid chlorides in nitrobenzene at 160°<sup>528</sup> or with chloromethylsulfonyl chloride.<sup>529</sup> The acetylated 4-methyl analog of maleic hydrazide has been also assigned as the *N*-acyl derivative on the basis of spectroscopic evidence.<sup>276</sup> Finally, *N*-acylated maleic hydrazides result from the rearrangement of the corresponding acylated *N*-aminomaleimides.<sup>278, 279</sup>

The Michael-type addition of maleic hydrazide to activated olefins has been investigated. Maleic hydrazide when treated with methyl acrylate, acrylonitrile, methyl vinyl ketone, and other activated olefins forms monoaddition products<sup>293, 528, 530</sup> for which the structure as *N*-substituted derivatives has been determined.<sup>293</sup> The exclusive formation of monoaddition products is in contrast to the saturated cyclic succinhydrazide which can form mono- and diaddition products.<sup>531</sup> Additions of the foregoing type are valid also for pyridazinones.<sup>164</sup> Low yields of addition products have been obtained when adding dihydropyran or its thio analog and dihydrofuran to pyridazinones or pyridazinethiones.<sup>532, 533</sup>

<sup>526</sup> A. Michaelis and R. Hermens, *Chem. Ber.* **26**, 674 (1893).

<sup>527</sup> J. Kinugawa, M. Ochiai, and H. Yamamoto, *Yakugaku Zasshi* **80**, 1559 (1960); *Chem. Abstr.* **55**, 10461 (1961).

<sup>528</sup> A. Le Berre, M. Dormoy, and J. Godlu, *Compt. Rend.* **261**, 1872 (1965).

<sup>529</sup> Z. El-Hewehi and F. Runge, *J. Prakt. Chem.* [4] **16**, 297 (1962).

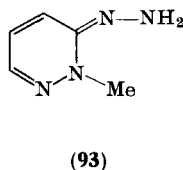
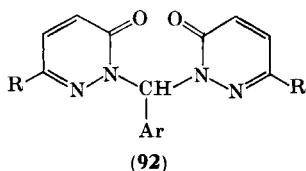
<sup>530</sup> E. Profft and R. Kaden, *Arch. Pharm.* **297**, 673 (1964).

<sup>531</sup> H. Feuer, G. B. Silverman, H. P. Angstadt, and A. R. Fauke, *J. Org. Chem.* **27**, 2081 (1962).

<sup>532</sup> H. Kühmstedt and G. Wagner, *Z. Chem.* **5**, 418 (1965).

<sup>533</sup> H. Kühmstedt and G. Wagner, *Z. Chem.* **5**, 269 (1965).

Hydroxymethylation and Mannich reaction have been performed with pyridazinones and maleic hydrazide, because they are acidic enough for these types of additions. Although it has been claimed that pyridazinones form only *N*-hydroxymethyl derivatives in the Mannich reaction<sup>534, 535</sup> it was reported that the corresponding Mannich bases are formed easily.<sup>536</sup> The substituted aminomethyl residue is attached always on the ring nitrogen. Mannich bases were likewise obtained from maleic hydrazide and its analogs, but not from its 2-phenyl



analog.<sup>536</sup> In the presence of alcohol and a small quantity of mineral acid maleic hydrazide reacts with formaldehyde to give the corresponding 2-alkoxymethyl derivatives.<sup>537</sup> They are also formed if a secondary amine is present. Two reaction paths have been presented to explain the above reaction.<sup>537</sup>

Condensation of 3(2*H*)-pyridazinones with aromatic aldehydes and acetic anhydride gives condensation products for which structures of type **92** have been assigned.<sup>534</sup>

Cyclic lactams do not normally form hydrazones or other derivatives typical for ketone carbonyl groups. However, 2-methyl-3(2*H*)-pyridazinone when treated with formylhydrazine and triethyl-oxonium fluoroborate afforded the hydrazone (**93**) which undergoes oxidative coupling to form azo dyes.<sup>502</sup> Oximes of 4(1*H*)-pyridazinones are also claimed to exist.<sup>236</sup>

1,2-Disubstituted 3,6-pyridazinediones show properties different from those of other pyridazinones which possess a more highly developed heteroaromatic character. The olefinic nature of the 4,5 double bond is evident from the ease of hydrogenation in the presence of palladium, the addition of bromine,<sup>291</sup> and additions of the Diels-Alder type.<sup>288</sup> Compounds of this type are also liable to acids or

<sup>534</sup> H. Gregory, J. Hills, and L. F. Wiggins, *J. Chem. Soc.*, 1248 (1949).

<sup>535</sup> U. M. Teotino and G. Cignarella, *Gazz. Chim. Ital.* **89**, 1200 (1959).

<sup>536</sup> H. Hellmann and I. Löschmann, *Chem. Ber.* **89**, 594 (1956).

<sup>537</sup> H. Feuer and R. Harmetz, *J. Org. Chem.* **24**, 1501 (1959).

alkalis. The molecule is split with acids into fumaric acid (via maleic acid) and a disubstituted hydrazine; with alkalis, however,  $N_1-C_6$  bond fission has been established.<sup>288</sup>

#### D. AMINOPYRIDAZINES

There are several routes which have been applied to the preparation of aminopyridazines. One of the commonest methods is the replacement of halogen atoms in the reaction with ammonia or amines. Halopyridazines are heated with concentrated ammonia, or, advantageously, with anhydrous ammonia in alcohol, or with amines under pressure at temperatures above  $100^\circ$ , usually about  $160^\circ$ , depending on the mobility of the halogen in the starting halo compound and the amine used. Thus, 3-amino-6-chloropyridazine is obtained from 3,6-dichloropyridazine upon heating with concentrated ammonia at  $100^\circ$  for 6 hours,<sup>429</sup> whereas 3-aminopyridazine is formed from 3-chloropyridazine with ethanolic ammonia at  $175^\circ$  after 3 hours.<sup>538</sup> Treatment of 4-chloro-3,6-dimethylpyridazine with ethylamine at  $120-130^\circ$  for 6 hours resulted in only 10% conversion.<sup>539</sup> Replacement of the chlorine atom at position 4 in 3(2*H*)-pyridazinones with these nucleophiles likewise requires temperatures over  $100^\circ$  or long reaction time.<sup>194</sup> As expected, bromopyridazines are usually more reactive than chloropyridazines.

The introduction of a second amino group by halogen replacement requires more drastic conditions. 3-Amino-6-chloropyridazine is converted into 3,6-diaminopyridazine in poor yield<sup>540</sup>; the reaction between 3,6-dichloropyridazine and most aliphatic amines stops at monosubstitution, but with aromatic amines 3-mono- and 3,6-disubstituted aminopyridazines have been obtained.<sup>541</sup> Similarly, 3-alkylamino-6-chloropyridazines failed to react with aniline<sup>541</sup> and 3,5-diamino-6-methoxypyridazine could not be produced from 3-amino-5-chloro-6-methoxypyridazine even at elevated temperatures.<sup>440</sup>

<sup>538</sup> G. W. Anderson, H. E. Faith, H. W. Marson, P. S. Winnek, and R. O. Roblin, *J. Am. Chem. Soc.* **64**, 2902 (1942).

<sup>539</sup> S. Sako, *Chem. Pharm. Bull. (Tokyo)* **11**, 337 (1963).

<sup>540</sup> T. V. Gortinskaya and M. N. Shchukina, *Zh. Obshch. Khim.* **30**, 1518 (1960).

<sup>541</sup> M. Kumagai, *Nippon Kagaku Zasshi* **82**, 227 (1961); *Chem. Abstr.* **56**, 10139 (1962).

Several simple aminopyridazines have been prepared by these amino-dechlorination reactions, such as 3-amino-,<sup>115, 426, 538</sup> 3-amino-6-methyl-,<sup>115, 117</sup> 3-amino-6-chloro-,<sup>427, 429, 542</sup> 3-aryl-amino-6-chloro-, or 3,6-diarylaminopyridazines<sup>541, 543</sup> and many other more complex aminopyridazines or pyridazones.<sup>115, 194, 272, 275, 286, 319, 429, 472, 544-551</sup>

Use of other aminating agents, such as urea, is also successful.<sup>128</sup> The Bucherer reaction gives aminopyridazines in low yield.<sup>552</sup> Amination of 3,6-dichloropyridazine with sodium amide, reported to provide 5-amino-3-chloropyridazine,<sup>553</sup> has been shown to give 6-chloro-3(2*H*)-pyridazinone in low yield together with recovered starting material.<sup>554</sup>

The exchange of halogens in 4-(or 5-)substituted 3,6-dihalopyridazines to produce the corresponding aminopyridazines has been already mentioned (Section IV, B), and, in addition to this, selective halogen replacement is observed with 3-bromo-6-chloro-4-(or 5)-methylpyridazine. Regardless of the halogen, dimethylamine attacks only at the position *meta* to the methyl group to form 3-bromo-6-dimethylamino-4-methylpyridazine or 3-chloro-6-dimethylamino-4-methylpyridazine, respectively.<sup>454</sup>

During aminolysis side reactions may occur, the most common being the solvolytic displacement of the halogen or methoxy group with the formation of pyridazinones or methoxypyridazines.<sup>117, 133, 453, 472</sup>

Another method of wide application is the hydrogenolysis of amino-halopyridazines over a catalyst, usually palladium on charcoal.

<sup>542</sup> E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.* **76**, 3225 (1954).

<sup>543</sup> F. Yoneda, Y. Ohtaka, and Y. Nitta, *Chem. Pharm. Bull. (Tokyo)* **11**, 740 (1963).

<sup>544</sup> I. Satoda, F. Kusada, and K. Mori, *Yakugaku Zasshi* **82**, 233 (1962).

<sup>545</sup> S. Sako, *Chem. Pharm. Bull. (Tokyo)* **11**, 261 (1963).

<sup>546</sup> T. Kuraishi, *Chem. Pharm. Bull. (Tokyo)* **6**, 331 (1958).

<sup>547</sup> D. I. Relyea, J. A. Riddell, and P. O. Tawney, *J. Med. Chem.* **6**, 807 (1963).

<sup>548</sup> R. Ratouis, J. R. Boissier, and C. Dumont, *J. Med. Chem.* **8**, 104 (1965).

<sup>549</sup> W. H. Nyberg and C. C. Cheng, *J. Heterocyclic Chem.* **1**, 1 (1964).

<sup>550</sup> J. R. Boissier, R. Ratouis, and C. Dumont, *J. Med. Chem.* **6**, 541 (1963).

<sup>551</sup> N. B. Chapman, K. Clarke, and K. Wilson, *J. Chem. Soc.*, 2256 (1963).

<sup>552</sup> H. Gregory, W. G. Overend, and L. F. Wiggins, *J. Chem. Soc.*, 2199 (1948).

<sup>553</sup> E. A. Steck, *J. Org. Chem.* **24**, 1597 (1959).

<sup>554</sup> W. E. Taft, J. Adams, and W. V. Curran, *J. Org. Chem.* **26**, 605 (1961).

Occasionally, this method is superior to the formation of aminopyridazines from monohalopyridazines, since aminolysis of polyhalopyridazines to aminohalopyridazines is easier to perform. Chloropyridazines with attached dimethylamino or methoxy groups are more easily dehalogenated compared with chloropyridazinones.<sup>296</sup> 3-Amino-,<sup>542</sup> 4-amino-,<sup>313, 448</sup> 3,4- or 3,5-diamino-,<sup>555</sup> 3-amino-4- (or 5-)methyl-,<sup>453</sup> 4-amino-3-methoxy-,<sup>445, 446, 458</sup> and 3-arylamino-pyridazines,<sup>543</sup> 4-(or 5-)amino-3(2*H*)-pyridazinone<sup>319, 546</sup> or its 2-methyl analogs,<sup>299</sup> and other more complex aminopyridazines or pyridazinones have been prepared by this method.

3,4,5-Triaminopyridazine<sup>555</sup> and 4,5-diamino-3-methoxy-6-methylpyridazine<sup>503</sup> have been prepared by reducing the 4-nitro group, but more common is the simultaneous catalytic reduction of the nitro and *N*-oxide groups of nitropyridazine-*N*-oxides (see Section IV, G).

Hydrogenolytic cleavage of the hydrazino group in hydrazino pyridazines in the presence of Raney nickel has been used particularly in connection with the synthesis of diaminopyridazines. Syntheses of 4-5-diamino-,<sup>555</sup> 3,4-diamino-5-(or 6-)chloro-,<sup>449, 556</sup> and 4-chloro-3,5-diaminopyridazine<sup>555</sup> or 5-amino-3(2*H*)-pyridazinone<sup>463</sup> and other aminopyridazines<sup>454</sup> have been performed in this manner.

The Hofmann reaction has been successfully applied to the synthesis of aminopyridazines in few cases.<sup>422, 446, 459, 557</sup> A simultaneous cyclization occurs when 6-methyl-3,4-pyridazinedicarboxamide is submitted to Hofmann reaction and a 2,4,5,6-tetraazanaphthalene derivative has been isolated.<sup>240</sup>

Other methods of minor importance include the displacement of a thio or alkylthio group with ammonia giving aminopyridazines in poor yield,<sup>552</sup> cleavage of a thiourethane with acid,<sup>235</sup> hydrogenolysis of isoxazolo[3,4-*d*]pyridazin-7-ones or 4,7-diones,<sup>558, 559</sup> or ring opening with acid of an imidazolo[4,5-*d*]pyridazine to yield 4,5-diamino-3,6-dimethoxypyridazine.<sup>560</sup>

Aminopyridazines exist predominantly in the amino form (Volume

<sup>555</sup> W. D. Guither, D. G. Clark, and R. N. Castle, *J. Heterocyclic Chem.* **2**, 67 (1965).

<sup>556</sup> G. A. Gerhardt and R. N. Castle, *J. Heterocyclic Chem.* **1**, 247 (1964).

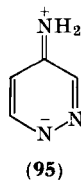
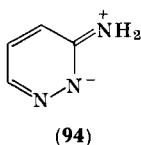
<sup>557</sup> C. M. Atkinson and R. E. Rodway, *J. Chem. Soc.*, 1 (1959).

<sup>558</sup> V. Sprio and E. Ajello, *Ric. Sci., Rend.* **A35**, 676 (1965).

<sup>559</sup> V. Sprio, E. Ajello, and A. Mazza, *Ric. Sci., Rend.* **36**, 196 (1966).

<sup>560</sup> T. Itai and S. Suzuki, *Chem. Pharm. Bull. (Tokyo)* **8**, 999 (1960).

1 of this Series, p. 408) and infrared spectroscopic examinations of 3- and 4-aminopyridazine and their *N*-deuterated analogs are in full agreement with the amino structure.<sup>561</sup> Furthermore, both structures involve resonance with the polar forms **94** and **95**, the contribution from the *p*-quinonoid type (**95**) being somewhat greater than from **94**, resulting in slight differences in the nature of the amino group in the isomeric aminopyridazines.



Aminopyridazines are considered to be monobasic and they behave in many reactions normally as expected for aromatic amines. They are monoacylated, but sometimes with acetic anhydride a neighboring halogen is also displaced to give the corresponding hydroxy- or acetoxyacetylaminopyridazines. Hence, acetylation of 3-amino-6-halopyridazine gives 3-amino-6-acetoxypyridazine,<sup>472</sup> 4-amino-3,6-dichloropyridazine afforded 4-acetamido-6-chloro-3(2*H*)-pyridazinone,<sup>546</sup> and 5-amino-3,4-dichloropyridazine yielded 5-acetamido-3-chloro-4(1*H*)-pyridazinone.<sup>319</sup> Simultaneous cyclization takes place when benzoylating 4-amino-3,6-dichloropyridazine to give 2-phenyl-6-chlorooxazolo[5,4-*c*]pyridazine.<sup>546</sup>

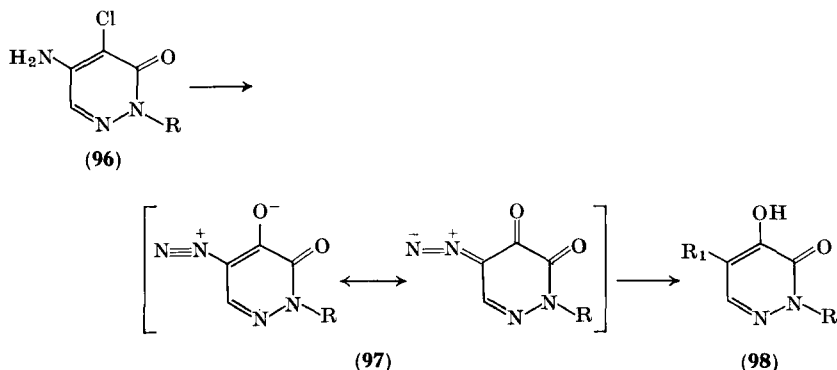
Aminopyridazines form nitraminopyridazines by controlled action of nitric acid.<sup>503, 540, 555, 562</sup> Reduction of the nitramino group to the hydrazino group could not be performed successfully and catalytic reduction yielded the starting aminopyridazine. The nitramino group can be displaced in a nucleophilic reaction with an amine,<sup>562</sup> and with mineral acid at elevated temperature the nitro group rearranges to the neighboring unsubstituted carbon of the pyridazine ring. In this way, introduction of a nitro group in the pyridazine nucleus is possible, for this diazine is otherwise resistant to electrophilic substitution even in the presence of activating groups. Syntheses of 3,5-diamino-4-nitro-<sup>555</sup> and 4-amino-3-methoxy-6-methyl-5-nitropyridazine<sup>503</sup> have

<sup>561</sup> Y. Nitta, R. Tomii, and F. Yoneda, *Chem. Pharm. Bull. (Tokyo)* **11**, 744 (1963).

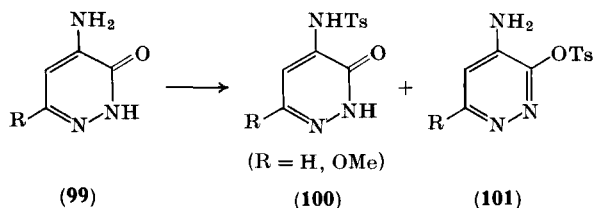
<sup>562</sup> S. Dixon and L. F. Wiggins, *J. Chem. Soc.*, 3236 (1950).



been accomplished in this way. Recently, direct nitration has been reported and with a mixture of potassium nitrate and sulfuric acid 4-amino-3-methoxy-6-methylpyridazine at room temperature<sup>503</sup> and 4-amino-3,6-dimethoxypyridazine at 315°<sup>560</sup> form the corresponding 5-nitro products.

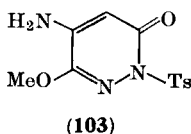
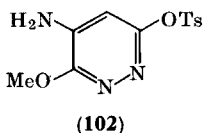


3-Aminopyridazines when diazotized form diazonium salts of various degrees of stability. Diazotized 3-amino-6-chloro-4-methylpyridazine evolves nitrogen at about 40–50°, whereas the diazotized 3-amino-6-chloro-5-methylpyridazine decomposes spontaneously at 0°. <sup>296</sup> 5-Amino-4-chloro-3(2H)-pyridazinones (96) behave differently

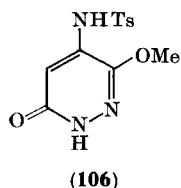
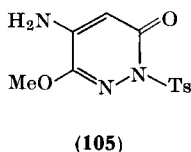
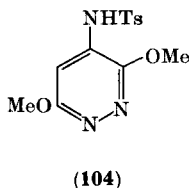


and besides diazotization the halogen is displaced by a hydroxyl group (97). The diazotized compound (97) can be reduced to the aminohydroxy derivative (98, R<sub>1</sub> = NH<sub>2</sub>), it can undergo the Sandmeyer reaction (98, R<sub>1</sub> = Cl), and it can be coupled with phenols.<sup>3</sup> Diazotization of 3,4-diamino-5-chloropyridazine led to *s*-triazolo-[4,5-*c*]pyridazine.<sup>556</sup>

Reaction of amino-3(2*H*)-pyridazinones and 4-amino-3,6-dimethoxy-3,4-dihydropyridazine with tosyl chloride has been investigated recently.<sup>562a</sup> Thus, 4-amino-3(2*H*)-pyridazinone (or its 6-methoxy analog) (**99**) when treated with tosyl chloride in pyridine at room temperature for several days yielded a mixture of **100** (R = OMe, 30%) and **101** (R = OMe, 24%; R = H, 1–2%). That **100** is formed by rearrangement



of the tosyl group from **101** has been confirmed in separate experiments. In contrast to these findings, 5-amino-6-methoxy-3(2*H*)-pyridazinone does not form products corresponding to **100**, and *O*-tosyl (**102**) and *N*<sub>2</sub>-tosyl (**103**) derivatives are formed in equal amounts. 4-Amino-3,6-dimethoxy-3,4-dihydropyridazine, when treated in an analogous way, afforded a mixture of three tosylated products: **104** (30–38%), **105** (14–16%), and **106** (1.3–2.6%).



The related hydrazinopyridazines are prepared almost exclusively by halogen displacement, temperatures of about 100° being usually satisfactory to bring about this reaction. The relatively easier replacement of a halogen in halopyridazines with hydrazine as compared to ammonia is certainly due to the fact that the former is a better nucleophile than the latter. Besides the differences in reactivity of unsymmetrically substituted 3,6-dihalopyridazines (Section IV, B), the preferential substitution of the 3-chlorine atom as compared to

<sup>562a</sup> T. Nakagome, A. Kobayashi, and A. Misaki, *Chem. Pharm. Bull. (Tokyo)* **14**, 1074 (1966).

the 4-(or 5-)chlorine atom is observed. 4-Amino-5-chloro-3-hydrazinopyridazine has been thus obtained isomer-free from 4-amino-3,5-dichloropyridazine and hydrazine hydrate and analogously 5-amino-4-chloro-3-hydrazinopyridazine is formed from 5-amino-3,4-dichloropyridazine.<sup>449</sup> As the introduction of a second hydrazino group by halogen exchange is more difficult, 3,6-dihydrazinopyridazine is better prepared from 6-mercapto-3(2*H*)-pyridazinethione<sup>429, 563</sup> or 3,6-dimethoxypyridazine<sup>540</sup> and hydrazine hydrate.

By the hydrazino-dechlorination method 3-hydrazino-,<sup>564</sup> 3-hydrazino-6-methyl-,<sup>149, 562, 565, 566</sup> 6-aryl-3-hydrazino-,<sup>149, 156, 164, 567</sup> 6-chloro-3-hydrazino-,<sup>429</sup> and 4-amino-5-hydrazinopyridazine<sup>555</sup> and other more complex hydrazinopyridazines<sup>3, 149, 156, 292, 433, 449, 454, 463, 556, 568, 569</sup> have been synthesized.

The hydrazino group of hydrazinopyridazines exhibits the normal characteristics of this group. Hydrazones or thiosemicarbazides can be prepared, with nitrous acid the corresponding azides are formed,<sup>3, 568</sup> or cyclization to tetrazolopyridazines may occur. 4-Azidopyridazine is prepared by deoxygenation of its *N*-oxide<sup>452</sup> and is catalytically reduced to 4-aminopyridazine. Reaction of hydrazinopyridazines with cyanamide or methylisothiurea has been used for the preparation of aminoguanidinopyridazines,<sup>565, 570</sup> as guanidinopyridazines are formed from aminopyridazines.<sup>570</sup> The hydrazino group can be replaced by hydrogen when a hydrazinopyridazine is heated in a solution of sodium carbonate in the presence of cupric oxide.<sup>3, 449</sup> Oxidation of hydrazinopyridazines with sodium hypohalite in strongly acidic solution causes substitution of the hydrazino group by chlorine (in hydrochloric acid) or hydroxyl (in sulfuric acid). Using sodium hypobromite or bromine in hydrobromic acid solution, the corresponding bromopyridazine is obtained.<sup>454, 455</sup> The reaction has been shown to proceed through an unstable diazonium intermediate.

<sup>563</sup> S. Sato, *Yakugaku Zasshi* **82**, 1085 (1962).

<sup>564</sup> T. Itai and S. Kamiya, *Chem. Pharm. Bull. (Tokyo)* **11**, 348 (1963).

<sup>565</sup> D. Shiho and N. Takahayashi, *J. Pharm. Soc. Japan* **75**, 776 (1955).

<sup>566</sup> H. H. Stroh, H. Hempel, and R. Apel, *Chem. Ber.* **98**, 2500 (1965).

<sup>567</sup> F. Gross, W. Schuler, J. Tripod, and R. Meier, *Experientia* **8**, 229 (1952).

<sup>568</sup> T. Itai and S. Kamiya, *Chem. Pharm. Bull. (Tokyo)* **11**, 1073 (1963).

<sup>569</sup> D. Libermann, N. Rist, F. Grumbach, M. Moyeux, B. Gauthier, A. Rouaix, J. Maillard, J. Himbert, and S. Cals, *Bull. Soc. Chim. France*, 1430 (1954).

<sup>570</sup> I. Zugravescu, M. Petrovanu, E. Rucinski, and M. Caprosu, *Rev. Roumaine Chim.* **10**, 641 (1965).

## E. PYRIDAZINECARBOXYLIC ACIDS

Pyridazinecarboxylic acids may be obtained by several methods common to other aromatic or heteroaromatic systems. Besides the direct synthesis of the acids by cyclization (Section III), several indirect methods are used. Variable yields have been reported for the pyridazinecarboxylic acids produced from oxidation reactions. Although no carboxylic acid could be obtained from oxidation of 3-methylpyridazine,<sup>161</sup> the oxidation of a methyl group attached to the pyridazine ring has led to the syntheses of 6-oxo-1,6-dihydro-3-,<sup>426</sup> 3-chloro-6-oxo-1,6-dihydro-4-(or 5-),<sup>453, 457</sup> 3-methoxy-6-oxo-1,6-dihydro-4-,<sup>459</sup> 3,6-dichloro-4-, and 3,6-dimethoxy-4-pyridazinecarboxylic acid,<sup>571</sup> and also 1-methyl-6-oxo-1,6-dihydro-3-pyridazinecarboxylic acid and its 4-chloro and 4,5-dichloro analogs.<sup>314</sup> Furthermore, oxidations of a *n*-butyl (syntheses of 3- or 4-pyridazinecarboxylic acid<sup>408, 572</sup>) or a hydroxymethyl (syntheses of 3-pyridazinecarboxylic acid<sup>573, 574</sup> and 4-oxo-1,4-dihydro-3,6-pyridazinecarboxylic acid<sup>351</sup>) and even an aryl or heteroaromatic group, as in the case of synthesis of 3-pyridazinecarboxylic acid<sup>11, 442</sup> and its 6-chloro analog,<sup>442</sup> or 4,5-pyridazinedicarboxylic acid,<sup>22</sup> have been achieved. 6-Phenyl-3-pyridazinecarboxylic acid has been synthesized from the corresponding aldehyde.<sup>421</sup> In the oxidation of alkylpyridazines most of the oxidizing agents probably function as hydride ion acceptors. Benzologs of pyridazine, such as cinnolines, phthalazines, or benzo[*c*]-cinnoline, have been oxidized to yield 5-aryl-3,4-pyridazinedicarboxylic acids,<sup>405, 557</sup> 4,5-pyridazinedicarboxylic acid,<sup>21, 575</sup> or 3,4,5,6-pyridazinetetracarboxylic acid.<sup>10</sup>

Another widely used method involves hydrolysis of cyanopyridazines. These are usually obtained from cyclizations of open-chain cyano compounds (synthesis of 4-cyano-3(2*H*)-pyridazinone and its methyl analogs<sup>267, 268</sup>), since replacement of a halogen atom by cyano group proceeds with pyridazines in low yields<sup>344</sup> or not at all. Many cyanopyridazines have been obtained by dehydration of amides, such as 3- or 4-cyanopyridazine,<sup>344, 573</sup> 3-chloro-6-cyanopyridazine or 6-cyano-2-methyl-3(2*H*)-pyridazinone,<sup>535</sup> and 3-chloro-4-cyano-

<sup>571</sup> T. Nakagome, *Yakugaku Zasshi* **83**, 934 (1963).

<sup>572</sup> G. Rosseels, *Ingr. Chimiste* **45**, 5 (1963).

<sup>573</sup> R. Delaby, R. Damiens, and M. Robba, *Compt. Rend.* **247**, 1739 (1958).

<sup>574</sup> W. J. Leanza, H. J. Becker, and E. F. Rogers, *J. Am. Chem. Soc.* **75**, 4086 (1953).

<sup>575</sup> H. Raistrick and P. Rudman, *Biochem. J.* **63**, 395 (1956).

6-methylpyridazine.<sup>576</sup> Cyanopyridazines are also conveniently prepared from pyridazine-*N*-oxides (Section IV, G).

Hydrolysis of cyanopyridazines is usually performed with sulfuric acid of high concentration at elevated temperatures (at about 150°). Syntheses of the following pyridazinecarboxylic acids have thus been achieved: 6-chloro-3-pyridazinecarboxylic acid,<sup>535</sup> 6-oxo-1,6-dihydro-5-<sup>267, 457</sup> or 3-pyridazinecarboxylic acid,<sup>577</sup> 6-phenyl-3-pyridazinecarboxylic acid,<sup>577</sup> 3-(and/or 4-)methyl-6-oxo-1,6-dihydro-5-pyridazinecarboxylic acid,<sup>268</sup> and 1,3,4-trimethyl-6-oxo-1,6-dihydro-5-pyridazinecarboxylic acid.<sup>578</sup> Hydrolytic conversion of a trichloromethyl group into a carboxylic acid has been used for the synthesis of  $\beta$ -(4-pyridazinyl)acrylic acid.<sup>277, 422</sup> Various methods for the synthesis of 3-pyridazinecarboxylic acid<sup>11, 442, 573, 574</sup> have been critically reviewed.<sup>572</sup>

Pyridazine side chain carboxylic acids are most conveniently prepared from open-chain compounds, as for example (6-oxo-1,6-dihydro-4-pyridazinyl)acetic<sup>277, 300</sup> or  $\beta$ -(6-oxo-1,6-dihydro-3-pyridazinyl)propionic acids<sup>579</sup> and derivatives.

Pyridazinecarboxylic acids in general have properties similar to those of pyridinecarboxylic acids and normal to the aromatic carboxyl group. Both isomeric pyridazine monocarboxylic acids are stronger acids than the corresponding pyridinecarboxylic acids. 3-Pyridazinecarboxylic acid ( $pK_a$  3.0) is a somewhat weaker acid than the isomeric 4-pyridazinecarboxylic acid ( $pK_a$  2.8).<sup>574</sup> The  $pK_a$  value for 4,5-pyridazinedicarboxylic acid is 3.30.<sup>418</sup> Infrared spectroscopy indicated that 3-chloro-6-oxo-1,6-dihydro-5-pyridazinecarboxylic acid exists in the chelated form in the crystalline state and that the isomeric 4-carboxylic acid forms intermolecular hydrogen bonds.<sup>580</sup> Hydrogen bonding is likewise evident from the examination of the crystal structure of 6-oxo-1,6-dihydro-3-pyridazinecarboxamide<sup>31, 32</sup> and the determined bond lengths have been used to calculate the double-bond character of this amide group.<sup>581</sup>

<sup>576</sup> A. Dornow and W. Abele, *Chem. Ber.* **97**, 3349 (1964).

<sup>577</sup> M. Ogata, *Chem. Pharm. Bull. (Tokyo)* **11**, 1522 (1963).

<sup>578</sup> P. Schmidt and J. Druey, *Helv. Chim. Acta* **40**, 1749 (1957).

<sup>579</sup> Y. Nakamura, T. Mizuno, I. Akamatsu, H. Iwashira, U. Hirahashi, and S. Tokuzumi, *Nippon Kagaku Zasshi* **86**, 424 (1965); *Chem. Abstr.* **65**, 709 (1966).

<sup>580</sup> T. Kuraishi, *Chem. Pharm. Bull. (Tokyo)* **6**, 551 (1958).

<sup>581</sup> T. Hahn, *Naturwissenschaften* **44**, 396 (1957).

Decarboxylation of pyridazinecarboxylic acids usually presents no difficulty and it has been carried out by heating the acid alone or in sulfuric acid, generally over 200°. Decarboxylation of 4,5-pyridazinedicarboxylic acid has been discussed earlier (Section II). Removal of both carboxyl groups has been performed with 3,6-diphenyl-4,5-pyridazinedicarboxylic acid<sup>228</sup> and 4-oxo-1,4-dihydro-3,6-pyridazine-dicarboxylic acid,<sup>351</sup> but more frequently stepwise decarboxylation is reported. The 4-carboxyl group is usually split off first from a 4,5-pyridazinedicarboxylic acid<sup>574</sup> or 6-oxo-1,6-dihydro-3,4-pyridazinedicarboxylic acid,<sup>307</sup> but not in the case of a 3,4-pyridazine-dicarboxylic acid where the 3-carboxyl is removed.<sup>22, 405, 557</sup>

Numerous derivatives of pyridazinecarboxylic acids, involving the carboxyl group, have been prepared. Pyridazinecarboxylic acid chlorides appear to be relatively unstable and few preparations are recorded.<sup>474, 535, 582</sup> It has been claimed that the ring nitrogen unsubstituted 6-oxo-1,6-dihydropyridazinecarboxylic acids cannot form acid chlorides.<sup>535</sup> Esterification of pyridazinecarboxylic acids presents no difficulties. Unusual lability is observed with esters of 1-phenyl-6-methyl-4-oxo-1,4-dihydropyridazine-5-carboxylic acid which are unstable and failed to give a disubstituted amide.<sup>474</sup> A variety of dialkylaminoalkyl esters, amides, and hydrazides have been synthesized,<sup>159, 498, 583-591</sup> particularly in connection with pharmacological evaluations.

<sup>582</sup> R. H. Wiley and C. H. Jarboe, *J. Org. Chem.* **21**, 256 (1956).

<sup>583</sup> T. V. Gortinskaya, K. M. Murav'eva, and M. N. Shechukina, *Zh. Obshch. Khim.* **25**, 2313 (1955).

<sup>584</sup> S. Hillers, E. A. Baumanis, G. P. Sokolov, and V. Ja. Grinstein, *Dokl. Akad. Nauk SSSR* **145**, 440 (1962).

<sup>585</sup> C. Pasini, A. Vercellone, and V. Erspamer, *Gazz. Chim. Ital.* **86**, 266 (1956).

<sup>586</sup> E. F. Rogers, W. J. Leanza, H. J. Becker, A. R. Matzuk, R. C. O'Neill, A. J. Basso, G. A. Stein, M. Solotorovsky, F. J. Gregory, and K. Pfister, *Science* **116**, 253 (1952).

<sup>587</sup> I. Satoda, N. Yoshida, and K. Mori, *Yakugaku Kenkyu* **28**, 609 (1956); *Chem. Abstr.* **51**, 16483 (1957).

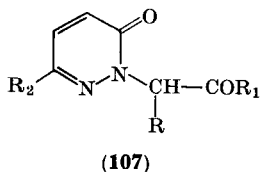
<sup>588</sup> J. Shavel, F. Leonard, F. H. McMillan, and J. A. King, *J. Am. Pharm. Assoc.* **42**, 402 (1953).

<sup>589</sup> G. Rosseels, G. Thuillier, and P. Rumpf, *Compt. Rend.* **255**, 1453 (1962).

<sup>590</sup> G. Rosseels, *Bull. Soc. Chim. Belges* **74**, 101 (1965).

<sup>591</sup> E. Kloimstein, R. Schönbeck, and H. Stormann, *Arzneimittel-Forsch.* **14**, 261 (1964).

Reduction of the carbethoxy group to the hydroxymethyl group with lithium aluminum hydride at  $-35^{\circ}$ <sup>576</sup> and Claisen condensation with ethyl acetate<sup>578</sup> are known to take place with pyridazinecarboxylic acids. 6-Oxo-1,6-dihydro-2-pyridazinyl aliphatic acids, having the pyridazinonyl residue attached at the  $\alpha$ -position of the aliphatic radical, readily undergo decarboxylative acylation with acid anhydrides in the presence of pyridine to form the corresponding 2-alkanones (107).<sup>499, 592</sup>



The methylene group of 6-oxo-1,6-dihydro-4-pyridazinylacetic acids is activated; it condenses with aldehydes and undergoes the Japp-Klingemann reaction.<sup>593</sup>

Other derivatives of minor importance, such as thioamides, amidoximes, iminoethers, and amidines have been prepared from the corresponding cyanopyridazines.<sup>344, 573, 578</sup>

## F. SULFUR COMPOUNDS OF PYRIDAZINE

Pyridazines with a potential mercapto group attached to the ring are prepared almost exclusively from the corresponding halopyridazines by conventional nucleophilic reaction with an alcoholic solution of KHS, formation of an isothiuronium salt with thiourea and decomposition of the latter with alkali, or treatment with  $P_4S_{10}$ . Formation of a mercaptopyridazine by use of ammonia and carbon disulfide is also reported in a particular case.<sup>527</sup> In general,  $P_4S_{10}$  converts pyridazinones into pyridazinethiones, and the thiourea or phosphorus pentasulfide pyridine methods seem to be advantageous

<sup>592</sup> F. H. McMillan, C. B. McMillan, K. A. Kun, and J. A. King, *J. Am. Chem. Soc.* **78**, 2642 (1956).

<sup>593</sup> A. Krbavčič and M. Tišler, *Monatsh. Chem.* **97**, 1494 (1966).

since best yields are thus obtained, in particular when preparing polymercaptopyridazines.<sup>449, 594, 595, 595a</sup> In general, greater reactivity of the halogen in halopyridazines toward the hydrosulfide ion as compared to hydroxide or alkoxide ions is due to the greater nucleophilicity of the former.

According to the methods outlined above, 3(2*H*)-,<sup>403</sup> 4(1*H*)-,<sup>492</sup> 6-methyl-,<sup>552, 595</sup> 6-chloro-,<sup>292, 429, 596, 597</sup> 6-bromo-,<sup>527</sup> 6-amino-,<sup>472, 595</sup> 6-hydroxy-,<sup>429</sup> 6-mercapto-,<sup>292, 429, 595-597</sup> 6-mercapto-4-methyl-,<sup>429</sup> 4-amino-6-chloro-,<sup>527</sup> and 6-methoxy-3(2*H*)-pyridazinethione<sup>597-599</sup> and other more complex pyridazinethiones<sup>235, 403, 423, 431, 440, 449, 462, 594, 595, 599</sup> have been synthesized. However, with the prolonged action of alkali, used for decomposing the isothiuronium salt prepared from 3,6-dichloropyridazine, the expected 6-mercapto-3(2*H*)-pyridazinethione is not isolated and instead bis(6-thioxo-3-pyridazinyl) sulfide has been obtained.<sup>471</sup>

Structural problems related to the potential mercapto group of pyridazines are similar to those of pyridazines with potential hydroxyl groups. The X-ray structure analysis of 3(2*H*)-pyridazinethione presented conclusive evidence that the thioamide form does in fact exist in the solid state.<sup>30</sup> The planar molecules of 3(2*H*)-pyridazinethione are arranged in layers forming dimers through hydrogen bonds between the NH group of one molecule and the thioamide sulfur atom of the second molecule. 6-Mercapto-3(2*H*)-pyridazinethione, the sulfur analog of maleic hydrazide, has been investigated with regard to its structure using ultraviolet and infrared spectroscopy and the monothiol-monothione form has been found to predominate in the solid state and in aqueous solutions.<sup>479, 480, 598-600</sup> Similarly, the predominance of the hydroxythione form of 6-hydroxy-3(2*H*)-pyridazinethione and that of the aminothione form of 6-amino-3(2*H*)-pyridazinethione has been established.<sup>599</sup>

<sup>594</sup> R. N. Castle and K. Kaji, *Tetrahedron Letters*, 393 (1962).

<sup>595</sup> R. N. Castle, K. Kaji, G. A. Gerhardt, W. D. Guither, C. Weber, M. P. Malm, R. R. Shoup, and W. D. Rhoads, *J. Heterocyclic Chem.* **3**, 79 (1966).

<sup>595a</sup> R. N. Castle, K. Kaji, and D. Wise, *J. Heterocyclic Chem.* **3**, 541 (1966).

<sup>596</sup> A. Pollak, B. Stanovnik, and M. Tišler, *Can. J. Chem.* **44**, 829 (1966).

<sup>597</sup> M. Kumagai, *Nippon Kagaku Zasshi* **81**, 1604 (1960).

<sup>598</sup> B. Stanovnik and M. Tišler, *Croat. Chem. Acta* **36**, 81 (1964).

<sup>599</sup> M. Fujisaka, Y. Ueno, H. Shinobara, and E. Imoto, *Bull. Chem. Soc. Japan* **37**, 1107 (1964).

<sup>600</sup> M. Kumagai, *Nippon Kagaku Zasshi* **81**, 1886 (1960).



$pK_a$  values of several pyridazinethiones have been determined (Table III); they are weaker bases than the oxoanalogs. This holds also for the *N*-methyl derivatives, while *S*-methyl derivatives are only slightly weaker bases than the methoxy analogs on account of the similar inductive effect of the methoxy and methylthio groups.<sup>492</sup>

TABLE III  
 $pK_a$  VALUES

Compound	Proton gain	Proton loss	
		First	Second
3(2 <i>H</i> )-Pyridazinethione <sup>a</sup>	-2.68	8.30	—
2-Methyl-3(2 <i>H</i> )-pyridazinethione <sup>a</sup>	-2.95	—	—
3-Methylmercaptopyridazine <sup>a</sup>	2.26	—	—
4(1 <i>H</i> )-Pyridazinethione <sup>a</sup>	-0.75	6.54	—
1-Methyl-4(1 <i>H</i> )-pyridazinethione <sup>a</sup>	-0.83	—	—
4-Methylmercaptopyridazine <sup>a</sup>	3.26	—	—
6-Mercapto-3(2 <i>H</i> )-pyridazinethione <sup>b</sup>	-0.5	2.1	10.4
3,6-Dimethylmercaptopyridazine <sup>b</sup>	-6.0	—	—
6-Hydroxy-3(2 <i>H</i> )-pyridazinethione <sup>b,c</sup>	-1.7	3.6	—
	-1.39	3.32	—
6-Methoxy-3(2 <i>H</i> )-pyridazinethione <sup>b,c</sup>	-2.3	—	—
	-2.36	6.95	—
3-Methylmercapto-6-methoxypyridazine <sup>c</sup>	1.84	—	—

<sup>a</sup> A. Albert and G. B. Barlin, *J. Chem. Soc.*, 3129 (1962).

<sup>b</sup> B. Stanovnik and M. Tišler, *Croat. Chem. Acta* **36**, 81 (1964).

<sup>c</sup> M. Fujisaka, Y. Ueno, H. Shinobara, and E. Imoto, *Bull. Chem. Soc. Japan* **37**, 1107 (1964).

In contrast to pyridazinones, pyridazinethiones are alkylated by alkylhalides exclusively on the exocyclic sulfur giving the *S*-alkylated derivatives, which are also accessible from halopyridazines and thiolates. The *N*-substituted pyridazinethiones are not obtainable by direct alkylations of pyridazinethiones, but can be prepared from the corresponding pyridazinones by the action of  $P_4S_{10}$ . 6-Mercapto-3(2*H*)-pyridazinethione and its analogs are alkylated likewise and 3,6-dialkylthiopyridazines are formed. With excess of the alkylating agent quaternization is expected, but this proceeds only with difficulty.<sup>403</sup> Under normal conditions 6-mercapto-3(2*H*)-pyridazinethione is *S,S*-dimethylated with dimethyl sulfate, but heating the

reaction mixture for one hour resulted in the formation of the *S,N*-dimethyl derivative also.<sup>600</sup> Most likely, a *S*→*N* rearrangement is operating, as observed in the methylation experiments with maleic hydrazide (Section IV, C). 6-Hydroxy-3(2*H*)-pyridazinethione and related compounds are *S*-alkylated<sup>509, 599, 601, 602</sup> to form 6-alkylthio-3(2*H*)-pyridazinones. Polymercaptopyridazines are usually easily mono- as well as polyalkylated and it is sometimes difficult to stop the alkylation at the monoalkylated stage.

Pyridazinethiones react with  $\alpha$ -acetobromoglucose and the tetraacetylated 1- $\beta$ -D-glucosyl residue is usually attached preferentially to the exocyclic sulfur; 2-(tetraacetyl-1- $\beta$ -D-glucosyl)-3(2*H*)-pyridazinethiones are also formed,<sup>235, 518, 523, 603, 604</sup> and are in some cases claimed to be the only products isolated.<sup>524</sup> As in the oxygenated series (Section IV, C), some *S*-glycosides have been rearranged under the influence of mercuric bromide into the *N*-glycosides.<sup>604, 605</sup> Acylations of pyridazinethiones proceed invariably at the sulfur atom and *S*-acyl derivatives are formed.<sup>429, 527, 600</sup>

6-Mercapto-3(2*H*)-pyridazinethione participates in addition reactions to systems with activated olefinic bonds or to quinones. In these reactions the mercapto group is involved and 6-*S*-substituted derivatives are formed.<sup>598, 606</sup> Hydroxymethylation and the Mannich reaction, investigated on pyridazinones, have been extended also to pyridazinethiones. 6-Mercapto-3(2*H*)-pyridazinethione forms a 2-hydroxymethyl-6-hydroxymethylthio derivative or the corresponding *N,S*-bis-Mannich base, while simple pyridazinethiones yield the mono-Mannich base with the substituted aminomethyl residue attached to the ring nitrogen at position 2.<sup>607</sup>

Pyridazinethiones and their *S*-alkylated analogs undergo many other reactions typical for these groups. The former are readily oxidized to disulfides by means of iodine, ferric chloride, or even iodobenzene<sup>608</sup> and in the presence of strong nitric acid they are

<sup>601</sup> N. Takahayashi, *J. Pharm. Soc. Japan* **76**, 1296 (1956).

<sup>602</sup> M. Ohta and K. Kishimoto, *Bull. Chem. Soc. Japan* **34**, 1402 (1961).

<sup>603</sup> G. Wagner and D. Heller, *Z. Chem.* **4**, 28 (1964).

<sup>604</sup> G. Wagner and D. Heller, *Arch. Pharm.* **299**, 481 (1966).

<sup>605</sup> G. Wagner and D. Heller, *Z. Chem.* **4**, 71 (1964).

<sup>606</sup> A. Pollak, B. Stanovnik, and M. Tišler, *Monatsh. Chem.* **97**, 1523 (1966).

<sup>607</sup> A. Pollak and M. Tišler, *Monatsh. Chem.* **96**, 642 (1965).

<sup>608</sup> H. Gregory, W. G. Overend, and L. F. Wiggins, *J. Chem. Soc.*, 2066 (1949).

oxidized to the sulfonic acids.<sup>609</sup> Thioethers have been oxidized to sulfoxides with hydrogen peroxide or peroxyacetic acid,<sup>439, 608, 609</sup> whereas permanganate oxidation led to sulfones.<sup>608, 609</sup> The latter are also obtained upon oxidations with peracids, such as peroxyacetic<sup>300, 497, 563, 600, 610</sup> or peroxyformic<sup>611</sup> acid, or with chlorine.<sup>549</sup>

There are few studies on the replacement of alkylthio by other groups. Nucleophilic substitution of the benzylsulfonyl group by sulfanilamide anion has been studied on 3-methoxy-6-benzylsulfonylpyridazine and demethylation, methylation, and nucleophilic replacement are possible. A mixture of four products results<sup>611</sup>; the methyl group transfer from a methoxyheterocycle to the sulfanilamide anion is of general applicability.<sup>612</sup> In the foregoing reaction demethylation predominates, whereas with the 6-methylsulfonyl analog the displacement of the methoxy group prevails (Volume 4, Chapter VI, p. 209).

Pyridazinethiones can be transformed into thiocyanatopyridazines with cyanogen bromide; the alternative method of preparation of these compounds, *viz.*, reaction of an alkali thiocyanate with a halo compound, gave lower yields in the case of chloropyridazines.<sup>613</sup>

Many attempts have been made to introduce a pyridazine ring into the structure of sulfa drugs, since Anderson *et al.*<sup>538</sup> had reported the synthesis and antibacterial activity of 3-sulfanilamidopyridazine. Two routes can be employed for this kind of pyridazine, *i.e.*, condensation of an arylsulfonyl chloride with an aminopyridazine in the presence of a base, usually pyridine, and reaction between an aryl-sulfonamide and a halopyridazine in the presence of bases at elevated temperatures. In this manner different 6-substituted 3-sulfanilylpyridazines, substituted at position 6 with hydrogen, hydroxy, alkoxy, halo, alkyl, acyl, mercapto, or alkylmercapto groups have been prepared.<sup>115, 117, 426, 427, 429, 435, 472, 538, 544, 552, 563, 611, 614, 615</sup> Sulfon-

<sup>609</sup> N. Takahayashi, *J. Pharm. Soc. Japan* **75**, 1245 (1955).

<sup>610</sup> N. Takahayashi, *J. Pharm. Soc. Japan* **76**, 1293 (1956).

<sup>611</sup> S. Kukolja, Z. Crnić, and D. Kolbah, *Tetrahedron* **19**, 1153 (1963).

<sup>612</sup> R. G. Shepherd, W. E. Taft, and H. M. Krazinski, *J. Org. Chem.* **26**, 2764 (1961).

<sup>613</sup> J. Kinugawa, M. Ochiai, and H. Yamamoto, *Yakugaku Zasshi* **83**, 767 (1963).

<sup>614</sup> T. Horie and T. Ueda, *Chem. Pharm. Bull. (Tokyo)* **10**, 595 (1962).

<sup>615</sup> J. H. Clark, J. P. English, G. R. Jansen, H. W. Marson, M. M. Rogers, and W. E. Taft, *J. Am. Chem. Soc.* **80**, 980 (1958).

amidopyridazines with other substituents or with the sulfonamido group at other positions of the pyridazine ring were similarly prepared.<sup>193, 299, 426, 445, 446, 458, 459, 544, 615-617</sup> Pyridazinethiones are converted by oxidative chlorination into the corresponding sulfonyl chlorides, which react with amines to give a different type of sulfonamide.<sup>618</sup>

### G. PYRIDAZINE *N*-OXIDES

With the *N*-oxidation of the pyridazine ring profound changes in properties and chemical reactivity result. Many reactions, otherwise difficult to carry out with pyridazines, are accomplished easily with their *N*-oxides. Since the oxygen atom of the *N*-oxide group is removable, new routes to otherwise inaccessible substituted pyridazines are available.

Two brief surveys concerning pyridazine *N*-oxides have been published recently.<sup>7, 619</sup>

#### 1. *Structure and Properties of Pyridazine N-Oxides*

The electronic structure of pyridazine mono-*N*-oxides has been calculated using a simple LCAO-MO method and disregarding overlap integrals and electronic interactions.<sup>620</sup> On the basis of  $\pi$  electron densities and calculated  $\pi$  moments it becomes evident that the  $\pi$  electron transfer from the oxygen atom to the pyridazine ring (1.23 D) is greater as compared to that of pyridine *N*-oxide (0.76 D). Thus the replacement of a ring carbon by the more electronegative nitrogen brings about a greater charge transfer from the *N*-oxide group to the ring. There is also a good agreement of the observed dipole moment of pyridazine *N*-oxide (5.21 D) with the calculated value (5.18 or 4.94 D).<sup>620</sup> Frontier electron densities have been also successfully applied to explain chemical reactivity of various pyridazine *N*-oxides, indicating that position 4 (para to the *N*-oxide group) should be the most reactive for electrophilic attack.

<sup>616</sup> T. Horie and T. Ueda, *Chem. Pharm. Bull. (Tokyo)* **10**, 591 (1962).

<sup>617</sup> M. Kumagai, and M. Bando, *Nippon Kagaku Zasshi* **84**, 995 (1963).

<sup>618</sup> V. Petelin-Hudnik, B. Stanovnik, and M. Tišler, *Arch. Pharm.* **299**, 646 (1966).

<sup>619</sup> G. Rosseels, *Ind. Chim. Belge* **31**, 668 (1966).

<sup>620</sup> T. Kubota and H. Watanabe, *Bull. Chem. Soc. Japan* **36**, 1093 (1963).

Dipole moment examinations proved useful in connection with structure determinations in a number of methyl-substituted or methylchloro-disubstituted pyridazine *N*-oxides.<sup>621, 622</sup> The calculated values for various mono- or disubstituted pyridazine *N*-oxides are in good agreement with the observed. Structures of several compounds, predicted on the basis of dipole moments, have later been confirmed by chemical transformations.

By far the best method for structure elucidations of substituted pyridazine *N*-oxides is nuclear magnetic resonance spectroscopy. A detailed study by two Japanese groups<sup>623, 624</sup> disclosed that pyridazine *N*-oxides give simple first-order spectra and this allows computation of all chemical shifts and coupling constants with sufficient accuracy by a first-order analysis. Because chloro and methyl groups exert little or no effect on the chemical shifts of the ring protons, chloro- and methyl-substituted pyridazine *N*-oxides have been used to assign the ring proton signals. NMR spectra of pyridazine *N*-oxide derivatives show a sequence  $H_3$  ( $\tau = 0.70$ – $1.65$ ) <  $H_6$  ( $\tau = 1.74$ – $2.05$ ) <  $H_5$  ( $\tau = 1.55$ – $3.05$ ) <  $H_4$  ( $\tau = 2.77$ – $3.43$ ) of shielding of ring protons. This order is in accordance with LCAO-MO calculations of the local  $\pi$  electron densities in the pyridazine *N*-oxide molecule, with the exception of the  $C_6$ -position. Charge density calculations indicate that the proton attached to  $C_6$  should be the most shielded. A possible explanation for this anomaly may be the diamagnetic anisotropy effect of the *N*-oxide group.

Chemical shifts of the methyl protons ( $\tau = 7.41$ – $7.64$ ) are in the sequence 3-methyl  $\simeq$  6-methyl < 5-methyl  $\simeq$  4-methyl and those of the methoxy group ( $\tau = 5.82$ – $6.07$ ) are in the sequence 3-methoxy < 6-methoxy < 4-methoxy. The spin-spin coupling constants are:  $J_{34} = 5.3$ – $6$ ,  $J_{35} = 2.0$ – $3.7$ ,  $J_{36} = 0.5$ – $1.0$ ,  $J_{45} = 8.0$ – $8.8$ ,  $J_{46} = 0.7$ – $1.0$ , and  $J_{56} = 5.8$ – $7.0$ . Long-range coupling constants between methyl protons and protons attached to the ortho ring carbon are smaller than 1 cps.

Other physicochemical methods, especially ultraviolet and infrared spectroscopy, have been useful in combination with chemical transformations for structure determination. Pyridazine *N*-oxides which

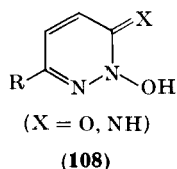
<sup>621</sup> H. Kano, M. Ogata, H. Watanabe, and I. Ishizuka, *Chem. Pharm. Bull. (Tokyo)* **9**, 1017 (1961).

<sup>622</sup> H. Watanabe, M. Ogata, and H. Kano, *Chem. Pharm. Bull. (Tokyo)* **11**, 39 (1963).

<sup>623</sup> Y. Kawazoe and S. Natsume, *Yakugaku Zasshi* **83**, 523 (1963).

<sup>624</sup> K. Tori, M. Ogata, and H. Kano, *Chem. Pharm. Bull. (Tokyo)* **11**, 235 (1963).

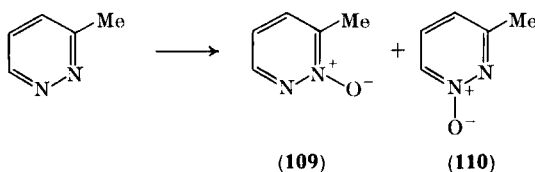
are able to enolize to compounds of type **108** develop deep blue or violet colors with  $\text{FeCl}_3$ .<sup>625</sup>



## 2. Syntheses

Peracids, such as performic, peracetic, perbenzoic, and monoperphthalic acid, or mixtures of hydrogen peroxide and the appropriate acid, have been used for *N*-oxidation of pyridazines.

Two isomeric *N*-oxides are expected to result from *N*-oxidation of unsymmetrically substituted pyridazines. So far, only mono-*N*-oxides are known in the pyridazine series, in contrast to cinnolines which also form 1,2-dioxides.<sup>626</sup>



Pyridazine *N*-oxide is formed in 89% yield when pyridazine is treated with hydrogen peroxide in glacial acetic acid.<sup>627</sup> 3-Methylpyridazine similarly gives a mono-*N*-oxide<sup>628</sup> for which the 2-oxide structure **(109)** has been ascribed.<sup>629</sup> Ogata and Kano<sup>630</sup> repeated this *N*-oxidation and were able to isolate the 2-oxide **(109)** and 1-oxide **(110)** in a ratio of 3:1. Likewise, 4-methylpyridazine yielded the corresponding 2-oxide and 1-oxide in a ratio of about 4:1.<sup>631</sup> The

<sup>625</sup> T. Itai and T. Nakashima, *Chem. Pharm. Bull. (Tokyo)* **10**, 347 (1962).

<sup>626</sup> I. Suzuki, M. Nakadate, N. Nakashima, and N. Nagasawa, *Tetrahedron Letters*, 2899 (1966).

<sup>627</sup> T. Itai and S. Natsume, *Chem. Pharm. Bull. (Tokyo)* **11**, 83 (1963).

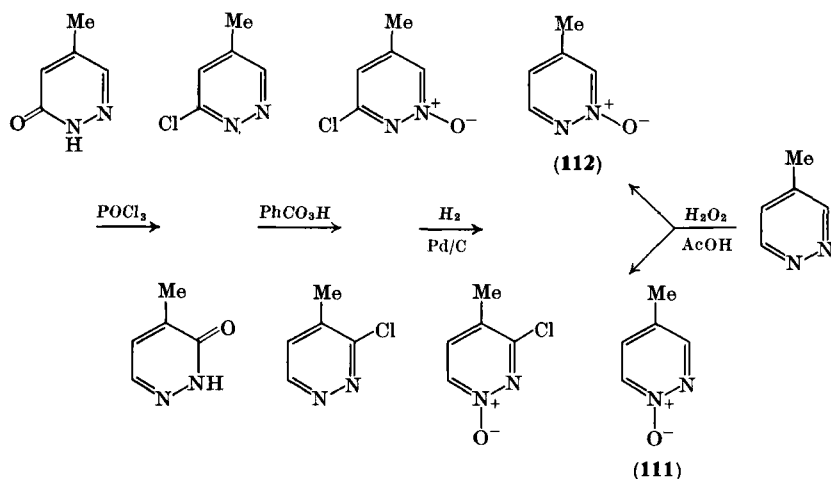
<sup>628</sup> M. Kumagai, *Nippon Kagaku Zasshi* **81**, 1148 (1960).

<sup>629</sup> T. Nakagome, *Yakugaku Zasshi* **81**, 1048 (1961).

<sup>630</sup> M. Ogata and H. Kano, *Chem. Pharm. Bull. (Tokyo)* **11**, 29 (1963).

<sup>631</sup> M. Ogata and H. Kano, *Chem. Pharm. Bull. (Tokyo)* **11**, 35 (1963).

structures of 4-methylpyridazine-1-oxide (**111**) and of 5-methylpyridazine-1-oxide (**112**) were proven by a sequence of reactions (Scheme 2).<sup>631</sup>



SCHEME 2

*N*-Oxidation of 3,4-dimethylpyridazine with hydrogen peroxide in acetic acid afforded some 2-oxide (16%) and more 1-oxide (36%),<sup>632</sup> whereas oxidation of 6-chloro-3,4-dimethylpyridazine with perbenzoic acid in chloroform produced 83% of 2-oxide and 0.7% of 1-oxide.<sup>632</sup> On the contrary, from 3,4-dimethyl-6-methoxypyridazine the corresponding 2-oxide was obtained as the sole product.<sup>632</sup> Likewise, only the 2-oxide was isolated from 3-methyl-6-chloropyridazine.<sup>629, 633</sup> From 4-chloro-3,6-dimethylpyridazine and mono-perphthalic acid, both isomeric *N*-oxides were isolated, the ratio of 1- and 2-oxide being 2:1.<sup>539</sup> Oxidation at  $\text{N}_2$  is reported in the case of 3-methyl-6-methoxypyridazine and 3-methyl-6(1*H*)-pyridazinone,<sup>633, 634</sup> 3-methyl-6-phenylpyridazine and 3-ethoxy-6-methylpyridazine.<sup>628</sup>

<sup>632</sup> T. Nakagome, *Chem. Pharm. Bull. (Tokyo)* **11**, 721 (1963).

<sup>633</sup> T. Nakagome, *Yakugaku Zasshi* **82**, 249 (1962).

<sup>634</sup> T. Nakagome, *Yakugaku Zasshi* **82**, 1206 (1962).

Hayashi *et al.*<sup>635</sup> showed that *N*-oxidation of monoalkoxydiazines with alkoxy groups attached to the ring carbon adjacent to one of the ring nitrogens always takes place at the nitrogen atom distant from the alkoxy group. This is explained as a result of steric hindrance by the alkoxy groups. An investigation of the geometrical arrangement of alkoxy substituents relating to the *N*-oxide group in pyridazine ring on the basis of dipole moment measurements<sup>636</sup> presented evidence for a *cis* arrangement, i.e., a conformation in which the attached alkyl group bends toward the nearby nitrogen atom.

3-Methoxypyridazine when treated with hydrogen peroxide in acetic acid yielded 3-methoxypyridazine 1-oxide,<sup>637, 638</sup> obtainable also by catalytic dehalogenation of 3-methoxy-6-chloropyridazine 1-oxide.<sup>638</sup> Similarly, *N*-oxidation of 3-ethoxypyridazine,<sup>445</sup> 3-benzyloxypyridazine,<sup>639</sup> and 3-alkoxy-6-chloropyridazines<sup>638</sup> yielded the corresponding 1-oxides. The 2-oxides, on the contrary, are formed from 6-methoxy-3-methyl-, 3-methyl-6-phenoxy-, and 6-ethoxy-3-methylpyridazine.<sup>629</sup> *N*-Oxidation of 3-chloro-6-methoxypyridazine produced a mixture of 3-chloro-6-methoxypyridazine 2-oxide, 6-chloro-3(2*H*)-pyridazinone, and 6-methoxy-3(2*H*)-pyridazinone.<sup>639</sup> The last two compounds are formed as a result of hydrolysis during the reaction. From 6-chloro-3-methoxy-4-(or 5-)methylpyridazine the corresponding 1-oxides are obtained.<sup>456</sup>

3,6-Dimethoxypyridazine,<sup>633, 640, 641</sup> 3,6-diethoxy-, and 3,6-dipropoxypyridazine<sup>640, 641</sup> are easily *N*-oxidized. In later oxidations of 3,6-dimethoxypyridazine, besides the corresponding *N*-oxide, 2,6-dimethyl-3(2*H*)-pyridazinone and 6-methoxy-3(2*H*)-pyridazinone, products of hydrolysis and rearrangement of the methyl group, have been isolated.<sup>642</sup> On the other hand, 4-methyl-3,6-dimethoxy- and 4-methyl-3,6-diethoxypyridazine gave a mixture of 1-oxide and 2-oxide under the same conditions,<sup>642</sup> contrary to what has been

<sup>635</sup> E. Hayashi, T. Higashino, C. Iijima, Y. Kono, and T. Doihara, *Yakugaku Zasshi* **82**, 584 (1962).

<sup>636</sup> H. Otomasu, H. Takahashi, and M. Ogata, *Chem. Pharm. Bull. (Tokyo)* **12**, 714 (1964).

<sup>637</sup> H. Igeta, *Chem. Pharm. Bull. (Tokyo)* **7**, 938 (1959).

<sup>638</sup> T. Itai and S. Sako, *Chem. Pharm. Bull. (Tokyo)* **10**, 989 (1962).

<sup>639</sup> T. Nakagome, *Yakugaku Zasshi* **82**, 244 (1962).

<sup>640</sup> T. Itai and H. Igeta, *J. Pharm. Soc. Japan* **75**, 966 (1955).

<sup>641</sup> T. Itai and S. Sako, *Chem. Pharm. Bull. (Tokyo)* **9**, 149 (1961).

<sup>642</sup> M. Yanai and T. Kinoshita, *Yakugaku Zasshi* **85**, 344 (1965).



reported earlier,<sup>456</sup> when 4-methyl-3,6-dimethoxypyridazine 1-oxide was obtained together with 6-methoxy-5-methyl-3(2*H*)-pyridazinone. Of other substituted 3,6-dimethoxypyridazines the 4-azido analog afforded only the corresponding 1-oxide,<sup>568</sup> but the 4-chloro analog gave a mixture of isomeric *N*-oxides together with an unidentified hydrolysis product.<sup>643</sup>

Oxidation of 4-methoxypyridazine has been carried out with hydrogen peroxide in acetic acid and a mixture of 4-methoxypyridazine 1-oxide (11%), 2-oxide (8%), and 4(1*H*)-pyridazinone (2%) was isolated,<sup>644</sup> the last compound resulting from hydrolysis. If the reaction temperature is raised to 100°, in addition to the foregoing three compounds 1-methyl-4(1*H*)-pyridazinone is formed in very low yield.<sup>644</sup> Of other alkoxy-pyridazines to be mentioned, 6-chloro-3,4-dimethoxypyridazine when oxidized with monoperphthalic acid yielded only the 1-oxide in 50% yield.<sup>644</sup>

Halopyridazines were likewise successfully *N*-oxidized. 3-Chloropyridazine gives the corresponding 1-oxide with perbenzoic acid,<sup>645</sup> whereas the isomeric 2-oxide is prepared indirectly by adding powdered copper to a diazotized solution of 3-aminopyridazine 2-oxide in hydrochloric acid.<sup>545</sup> After earlier reported<sup>610, 646</sup> failures to prepare 3,6-dichloropyridazine *N*-oxide from 3,6-dichloropyridazine and hydrogen peroxide in acetic acid [6-chloro-3(2*H*)-pyridazinone was isolated due to hydrolysis], the desired *N*-oxide was later obtained in low yield.<sup>638, 647</sup> The yield of 3,6-dichloropyridazine *N*-oxide can be improved when using monoperphthalic acid in ethereal solution<sup>638</sup> or perbenzoic acid in chloroform.<sup>639</sup>

Other, more complex halopyridazine *N*-oxides are known. 5-Amino-3,4- and 4-amino-3,5-dichloropyridazine form the corresponding 1-oxide,<sup>648</sup> but 3,6-dichloro-4-methoxypyridazine is oxidized with monoperphthalic acid in ethereal solution to yield a mixture of the 1-oxide (12%), 2-oxide (5%), and 6-chloro-4-methoxy-3(2*H*)-pyridazinone and 6-chloro-4-methoxy-3(2*H*)-pyridazinone (up to 7%).<sup>644</sup>

Of aminopyridazines, the 3 isomer gives a resin with monoperphthalic acid,<sup>625</sup> while the 2-oxide resulted from oxidation with

<sup>643</sup> M. Yanai and T. Kinoshita, *Yakugaku Zasshi* **86**, 314 (1966).

<sup>644</sup> T. Itai and S. Natsume, *Chem. Pharm. Bull. (Tokyo)* **10**, 643 (1962).

<sup>645</sup> H. Igeta, *Chem. Pharm. Bull. (Tokyo)* **8**, 559 (1960).

<sup>646</sup> H. Euler, H. Hasselquist, and O. Heidenberger, *Arkiv. Kemi* **14**, 419 (1959).

<sup>647</sup> F. Yoneda and Y. Nitta, *Chem. Pharm. Bull. (Tokyo)* **11**, 269 (1963).

<sup>648</sup> S. Sako, *Chem. Pharm. Bull. (Tokyo)* **14**, 303 (1966).

hydrogen peroxide in acetic acid.<sup>625,649</sup> 3-Acetamidopyridazine 2-oxide and 1-oxide (82 and 2%)<sup>625</sup> were obtained using mono-perphthalic acid, whereas hydrogen peroxide in acetic acid gave 33 and 10% of the corresponding oxides<sup>649</sup> from 3-acetamidopyridazine.

3-Ethylaminopyridazine 2-oxide,<sup>545</sup> 3-amino-6-chloropyridazine 2-oxide,<sup>649-651</sup> and ethyl 3-carbamato-6-chloropyridazine 2-oxide<sup>625,649</sup> have been obtained by *N*-oxidation of the corresponding pyridazines. The 2-oxide results also from 3-acetamido-6-methoxypyridazine<sup>650,651</sup> and the former can be hydrolyzed to 3-amino-6-methoxypyridazine 2-oxide.<sup>650</sup> This can in turn be prepared by three independent syntheses starting from ethyl 3-carbamato-6-methoxypyridazine (*N*-oxidation and subsequent hydrolysis),<sup>650</sup> from 3-nitro-6-methoxypyridazine 2-oxide by reducing the nitro group,<sup>652</sup> or by direct *N*-oxidation of 3-amino-6-methoxypyridazine.<sup>650</sup> Other 3-acetamido-6-alkoxypyridazines readily form the 2-oxides,<sup>650</sup> whereas 3-acetamido-6-chloropyridazine is only with difficulty converted into its 2-oxide.<sup>650</sup>

### 3. Reactions

*a. Nitration.*  $\alpha$ - and  $\gamma$ -positions relative to the *N*-oxide group of pyridazine *N*-oxides are prone to electrophilic attack on account of the mesomeric effect of the *N*-oxide group. Thus, the introduction of substituents at these positions is possible by electrophilic substitution.

Nitration of pyridazine 1-oxide (**113**,  $R = R_1 = H$ )<sup>627,653</sup> and many of its 3- or 6-substituted and 3,6-disubstituted analogs (**113**,  $R$  and/or  $R_1 = \text{alkyl, alkoxy, or chloro}$ )<sup>630,653</sup> with a mixture of fuming nitric and concentrated sulfuric acid afforded the corresponding 4-nitropyridazine 1-oxide derivatives (**114**). Under similar reaction conditions nitration of 3-methylpyridazine 1-oxide could not be accomplished and even after 6 hours at 100° starting material was recovered,<sup>630</sup> whereas 3-methylpyridazine 2-oxide is nitrated to give 3-methyl-5-nitropyridazine 2-oxide in excellent yield.<sup>630,653</sup>

<sup>649</sup> T. Itai and T. Nakashima, *Chem. Pharm. Bull. (Tokyo)* **10**, 936 (1962).

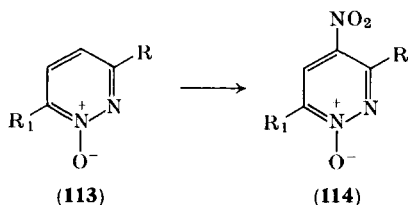
<sup>650</sup> T. Horie and T. Ueda, *Chem. Pharm. Bull. (Tokyo)* **11**, 114 (1963).

<sup>651</sup> T. Horie, *Yakugaku Zasshi* **82**, 627 (1962).

<sup>652</sup> T. Nakagome, *Yakugaku Zasshi* **81**, 554 (1961).

<sup>653</sup> T. Nakagome, *Yakugaku Zasshi* **82**, 253 (1962).

There are some diversities in results concerning the nitration of 3-methoxypyridazine 1-oxide. According to one report<sup>654</sup> 3-methoxy-4-nitropyridazine 1-oxide and 3-methoxy-4,6-dinitropyridazine 1-oxide were isolated, while another<sup>652</sup> describes three products: a molecular compound of 3-methoxypyridazine 1-oxide with 3-methoxy-4-nitropyridazine 1-oxide, 3-methoxy-6-nitropyridazine 1-oxide, and 3-methoxy-6-nitropyridazine. The complex can be separated into its components with acid or by chromatography.<sup>652</sup> In contrast, 3-ethoxypyridazine 1-oxide afforded the 4-nitro derivative as the sole product.<sup>445</sup>



4-Methylpyridazine 1-oxide and 6-chloro-3,4-dimethylpyridazine 1-oxide remained unaffected by the nitrating mixture,<sup>631, 632</sup> but the corresponding 2-oxides could be nitrated to give 4-methyl-5-nitropyridazine 2-oxide<sup>631</sup> and presumably 6-chloro-3,4-dimethyl-5-nitropyridazine 2-oxide.<sup>632</sup> 3-Methoxy-4-methylpyridazine 1-oxide<sup>456</sup> and 3,4-dimethylpyridazine 1-oxide,<sup>655</sup> where the  $\gamma$ -position relative to the *N*-oxide group is substituted, are nitrated in the  $\alpha$ -, i.e., 6-position. The replacement of the 3-methoxy group by the methyl group results in a decrease in the reactivity of the 6-position and 6-nitro-3,4-dimethylpyridazine 1-oxide is obtained in low yield (9%); 3-methylpyridazine 1-oxide afforded the 4-nitro derivative only, under even more vigorous reaction conditions.<sup>655</sup> Other examples of nitrations of pyridazine *N*-oxides involve the synthesis of 3-acetamido-6-alkoxy-5-nitropyridazine 2-oxides,<sup>440</sup> 3,4-dimethyl-5-nitropyridazine 2-oxide and its 6-chloro and 6-methoxy analogs,<sup>655</sup> as well as 3,6-dimethoxy-4-nitropyridazine 1-oxide,<sup>654</sup> 6-chloro-3-methoxy-4-nitropyridazine 1-oxide, 6-chloro-4-nitro-3(2*H*)-pyridazinone 1-oxide,<sup>656</sup> and 3-methyl-4-nitropyridazine 1-oxide.<sup>655</sup>

However, if nitration of pyridazine *N*-oxides is carried out with silver nitrate in the presence of an acid chloride the reaction takes

<sup>654</sup> H. Igeta, *Chem. Pharm. Bull. (Tokyo)* **8**, 550 (1960).

<sup>655</sup> T. Nakagome, *Chem. Pharm. Bull. (Tokyo)* **11**, 726 (1963).

<sup>656</sup> T. Itai and S. Sako, *Chem. Pharm. Bull. (Tokyo)* **10**, 933 (1962).

another course. Under such conditions, the reaction takes place at the meta position relative to the *N*-oxide group and only mononitrated products are formed. If both meta positions are unsubstituted, a mixture of both possible isomers is usually produced. Thus, pyridazine *N*-oxide, with silver nitrate and benzoyl chloride, gives a mixture of 3-nitropyridazine 1-oxide (33%) and 5-nitropyridazine 1-oxide (0.8%).<sup>657</sup> Likewise, from 3-methylpyridazine 1-oxide and 3-methoxy-pyridazine 1-oxide the corresponding 5-nitro derivatives have been obtained (12 or 11%, respectively), but 3,6-dimethylpyridazine 1-oxide gave, besides the corresponding 5-nitro derivative (25%), some 6-cyano-3-methylpyridazine 1-oxide.<sup>658</sup>

*b. Nucleophilic Substitutions.* The most important nucleophilic substitutions of pyridazine *N*-oxides include the replacement of a halogen or nitro group.

In general, the chlorine atom at position 3 in 3,6-dichloropyridazine 1-oxide is more reactive than that at position 6 for nucleophilic displacement.<sup>660</sup> No difference in the reactivity of the 3- and 6-chlorine in the corresponding monochloropyridazine 1-oxides has been observed<sup>645</sup> and 4-chloro-3,6-dimethylpyridazine 1-oxide is less reactive than 5-chloro-3,6-dimethylpyridazine 1-oxide.<sup>659</sup> A study of the replacement of the halogen in 3-, 4-, 5-, and 6-chloropyridazine 1-oxides, 4- and 5-chloro-3,6-dimethylpyridazine 1-oxides, and 3- and 4-bromopyridazine 1-oxides with piperidine and the reaction between 3- and 4-chloropyridazine 1-oxides and sodium ethoxide has been undertaken in order to establish the reactivity of individual halogens. In the reaction of chloropyridazine 1-oxides with piperidine the rate order of position reactivity has been found to be  $5 > 3 > 6 > 4$  and the rate ratios were  $41 : 18 : 5.6 : 1$  at  $50^\circ$ .<sup>661</sup> In the case of 5-chloro-3,6-dimethylpyridazine 1-oxide and the less reactive 4-chloro analog the rate ratio was  $45 : 1$ .<sup>661</sup> Similar results have been observed from reactions with sodium methoxide. As the variation of entropy of activation is small,<sup>661</sup> except for 4- and 5-chloro-3,6-dimethylpyridazine 1-oxides, the results indicate that the combined effect of a

<sup>657</sup> T. Itai and S. Natsume, *Chem. Pharm. Bull. (Tokyo)* **11**, 342 (1963).

<sup>658</sup> T. Itai and S. Natsume, *Chem. Pharm. Bull. (Tokyo)* **12**, 228 (1964).

<sup>659</sup> H. Igeta, *Chem. Pharm. Bull. (Tokyo)* **8**, 368 (1960).

<sup>659a</sup> M. Ogata, H. Kano, and K. Tori, *Chem. Pharm. Bull. (Tokyo)* **11**, 1527 (1963).

<sup>660</sup> S. Sako, *Chem. Pharm. Bull. (Tokyo)* **10**, 956 (1962).

<sup>661</sup> S. Sako and T. Itai, *Chem. Pharm. Bull. (Tokyo)* **14**, 269 (1966).

meta *N*-oxide and an ortho or para nitrogen is greater than that of a meta nitrogen and an ortho or para *N*-oxide.

In general, the replacement of chlorine is possible with an alkoxy,<sup>440, 452, 539, 545, 630, 639, 640, 643, 644, 650, 651, 656, 657, 660, 662</sup> amino,<sup>657</sup> ethylamino,<sup>545</sup> piperidino,<sup>660</sup> hydrazino,<sup>452, 657</sup> azido,<sup>452, 564</sup> hydroxylamino,<sup>657</sup> mercapto,<sup>663</sup> methylmercapto,<sup>651, 662</sup> or methylsulfonyl group.<sup>662</sup>

3,6-Dichloropyridazine 1-oxide produces usually in these reactions a mixture of both isomers. With sodium ethoxide, 6-chloro-3-ethoxypyridazine 1-oxide (72%) and 3-chloro-6-ethoxypyridazine 1-oxide (11%) have been isolated. The reaction with sodium methoxide proceeds similarly to give the 3-methoxy (80%) and 6-methoxy (7.5%) analog, but with sodium propoxide only 6-chloro-3-propoxypyridazine 1-oxide has been obtained.<sup>660</sup> Ethylamine reacted to give a mixture of 6-chloro-3-ethylaminopyridazine 1-oxide (54%) and 3-chloro-6-ethylaminopyridazine 1-oxide (14%), whereas in the reaction with piperidine the 3-piperidino analog was formed in 60% yield together with 11.5% of 3,6-dipiperidinopyridazine 1-oxide.<sup>660</sup> Only the 3-chlorine atom of 3,6-dichloropyridazine 1-oxide can be substituted with an azido group,<sup>564</sup> and it has been reported that no replacement of the halogen by a methoxy group is possible in 4-chloro-3,6-dimethoxypyridazine 1-oxide.<sup>640, 659</sup>

Another large group of nucleophilic replacements involves the nitro group in pyridazine *N*-oxides. One or two nitro groups at positions 3, 4, 5, or 6 in the pyridazine *N*-oxide ring are easily substituted with chlorine when nitropyridazine *N*-oxides are heated with acetyl chloride in chloroform solution<sup>440, 539, 630, 656–659, 664</sup> or with 15–20% hydrochloric acid.<sup>440, 630, 658</sup> In the last-mentioned procedure acetamido groups are hydrolyzed, if present.<sup>440</sup> The nitro group can likewise be replaced with bromine on heating with hydrobromic acid.<sup>648</sup>

The yields in the reactions of nitropyridazine *N*-oxides with acetyl chloride or hydrochloric acid are usually similar. However, certain polysubstituted nitropyridazine *N*-oxides behave differently in these reactions. 3,6-Dimethyl-5-nitropyridazine 1-oxide reacts with hydrochloric acid to yield the 5-chloro derivative in 69% yield,

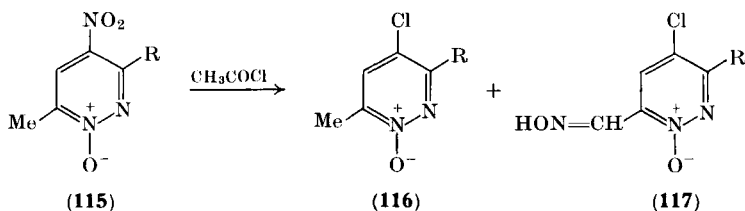
<sup>662</sup> H. Nishimura, H. Kano, K. Tawara, M. Ogata, and Yu. Tanaka, *Shionogi Kenkyusho Nempo* **14**, 86 (1964).

<sup>663</sup> T. Irikura, K. Shirai, and S. Sato, *Yakugaku Zasshi* **84**, 793 (1964).

<sup>664</sup> M. Ogata, *Chem. Pharm. Bull. (Tokyo)* **11**, 1511 (1963).

whereas with acetyl chloride the latter is formed in only 9% yield, together with 5-chloro-6-cyano-3-methylpyridazine 1-oxide (60%).<sup>658</sup> Refluxing 3-methyl-5-nitropyridazine 1-oxide in concentrated hydrochloric acid yielded 5-chloro-3-methylpyridazine 1-oxide in 7% yield, whereas with acetyl chloride this is raised to 63%.<sup>658</sup>

An interesting reaction is that between 6-methyl-4-nitropyridazine 1-oxide or its 3-substituted analogs (**115**) and acetyl chloride. Along with the expected 4-chloro derivatives (**116**)<sup>624</sup> other products were isolated and later identified as 3-substituted 4-chloro-6-formylpyridazine 1-oxide oximes (**117**).<sup>664</sup>



Chloro or nitro groups at position 4 possess a greater reactivity than chlorine at position 6. Thus, the reaction of 6-chloro-3-methoxy-4-nitropyridazine 1-oxide with acetyl chloride yields 4,6-dichloro-3-methoxypyridazine 1-oxide, which when heated with sodium methoxide produces 6-chloro-3,4-dimethoxypyridazine 1-oxide.<sup>656</sup>

The nitro group can also be replaced by methoxy<sup>456, 627, 630, 637, 643, 653, 654, 656-658</sup> or phenoxy<sup>657</sup> groups in the reaction with sodium methoxide or phenoxide. There are also some anomalies, as for example the unreactivity of the nitro group in 6-alkoxy-3-amino-5-nitropyridazine 2-oxides while methoxy-dechlorination takes place with the corresponding 5-chloro compound.<sup>440</sup> On the other hand, the nitro group of 3,6-dimethoxy-4-nitropyridazine 1-oxide is normally replaced in the reaction with methoxide, whereas the chlorine atom of the corresponding 4-chloro analog is unreactive.<sup>640, 659</sup>

Amino groups at the 3-, 4-, 5-, or 6-positions in pyridazine 1-oxides have been successfully replaced by chlorine or bromine in the Gattermann reaction,<sup>539, 545, 647, 648</sup> but yields of 3-chloro (or bromo) derivatives are low.<sup>648</sup> As there are no other suitable methods, this reaction provides the most convenient synthesis of 5- and 6-halopyridazine 1-oxides. In this manner 3-, 4-, 5-, and 6-bromopyridazine

1-oxides have been prepared from the corresponding aminopyridazine 1-oxides,<sup>648</sup> 3,4,5-trichloropyridazine 1-oxide from 4-amino-3,5-dichloropyridazine 1-oxide,<sup>648</sup> 3,6-dichloropyridazine 1-oxide from the 6-amino analog,<sup>647</sup> 4-chloro-3,6-dimethylpyridazine 1-oxide from the 4-amino analog,<sup>539</sup> and 3-chloropyridazine 2-oxide from 3-aminopyridazine 2-oxide.<sup>545</sup>

There are individual cases of replacement of other groups in substituted pyridazine *N*-oxides, such as the substitution of methoxy or ethoxy groups with amino or hydrazino groups,<sup>452, 564</sup> and replacement of an azido group with a methoxy, ethoxy, or benzyloxy group.<sup>452, 564, 568</sup>

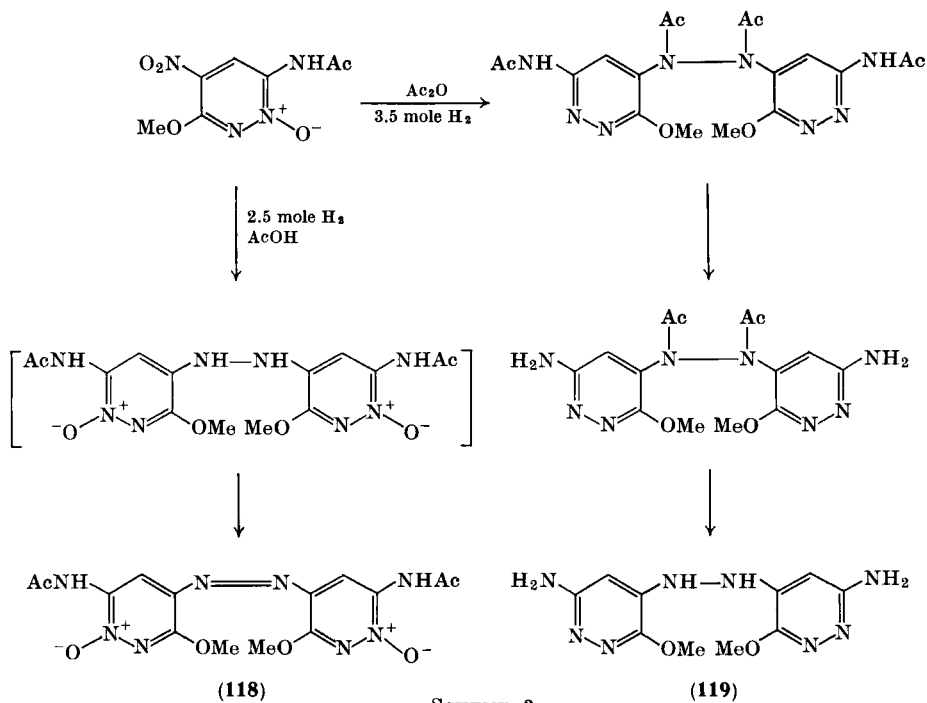
*c. Deoxygenation and Reduction of Pyridazine N-oxides.* Hydrogenation of nitropyridazine *N*-oxides can give rise to the corresponding aminopyridazine *N*-oxides if the reaction is performed at normal pressure and in the presence of palladized charcoal in alcoholic or acetic acid solution. Reduction may proceed with controlled addition of hydrogen to the stage of the corresponding amine<sup>440, 456, 630, 652-654, 657, 659</sup> or hydroxylamine.<sup>440, 657</sup> If halogen is present, dehalogenation takes place simultaneously.<sup>659</sup>

Bimolecular reduction products have been isolated when hydrogenating 3-acetamido-6-methoxy-5-nitropyridazine 2-oxide over palladized charcoal.<sup>440</sup> Depending on the solvent used and the amount of hydrogen absorbed, two different products, **118** and **119**, have been isolated (Scheme 3).

Hydrogenolysis of the halogen in chloropyridazine *N*-oxides is readily achieved with hydrogen in the presence of palladium on charcoal, usually in an alcoholic solution.<sup>456, 568, 564, 629, 631, 637, 644, 649, 651, 659</sup> At the same time a nitro group, if present, is reduced to amino group.<sup>659</sup> Aminopyridazine *N*-oxides result also from the reduction of the corresponding azides with hydrogen over palladized charcoal in the presence of traces of ammonia.<sup>452, 564, 568</sup>

Simultaneous reduction of a nitro to an amino group and deoxygenation of the *N*-oxide group can be accomplished with hydrogen in the presence of Raney nickel or palladium on charcoal. In several cases Raney nickel was used<sup>456, 503, 560, 627, 652-655</sup> and dehalogenation may also occur at the same time. Palladized charcoal in methanolic or dilute aqueous hydrochloric acid has been used to bring about the same transformations.<sup>445, 630, 631, 655, 657</sup> A particular case is 4-chloro-3,6-dimethoxypyridazine 1-oxide which is not deoxygenated with either Raney nickel and hydrogen or phosphorus trichloride.<sup>659</sup>

Phosphorus trichloride is also very useful for deoxygenation of pyridazine *N*-oxides,<sup>452, 539, 630, 643, 659</sup> and with phosphorus oxychloride simultaneous deoxygenation and chlorination of the pyridazine nucleus take place. The chlorine atom enters at the position



SCHEME 3

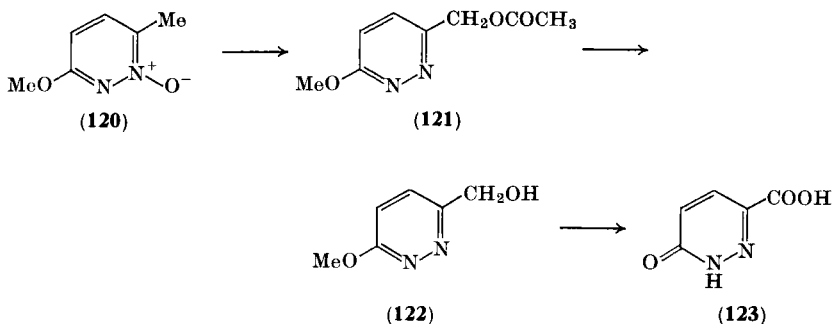
ortho or para to the original *N*-oxide group.<sup>440, 445, 539, 630, 637, 659</sup> This method thus represents a convenient synthesis of 4-chloro-3,6-disubstituted pyridazines. In this way, 3-amino-(or acetamido)-6-alkoxy-pyridazine 2-oxides are transformed into 3-amino-(or acetamido)-6-alkoxy-5-chloropyridazines in low yields,<sup>440</sup> 3-methyl-6-methoxypyridazine 2-oxide is converted into 5-chloro-6-methoxy-3-methylpyridazine,<sup>630</sup> and 3,6-dimethoxypyridazine 1-oxide forms 4-chloro-3,6-dimethoxypyridazine.<sup>659</sup>

With pyridazine *N*-oxides with an unsubstituted ortho position, the reaction with phosphorus oxychloride seems to give primarily the ortho chloro-substituted pyridazine. 3-Methoxypyridazine 1-oxide thus gives 3-chloro-6-methoxypyridazine.<sup>637</sup>



There are only two examples of attempted side chain bromination of pyridazine *N*-oxides. 3-Methoxy-5-methylpyridazine 1-oxide did not react with *N*-bromosuccinimide, but 3-methoxy-6-methylpyridazine 1-oxide yielded 6-bromomethyl-3-methoxypyridazine 1-oxide.<sup>659a</sup>

*d. Group Rearrangements.* Heating of pyridazine *N*-oxides in acetic anhydride causes transfer of the oxygen atom from the *N*-oxide group to the vicinal ring carbon. The ortho position may be unsubstituted



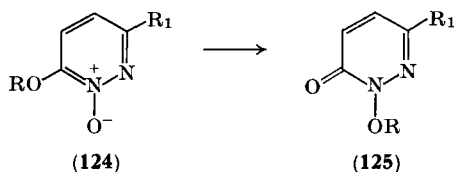
or contain a methyl group. Thus, 3-aminopyridazine 1-oxide is converted with acetic anhydride and subsequent hydrolysis to 6-amino-3(2*H*)-pyridazinone.<sup>650</sup> A similar treatment of 6-methoxy-3-methylpyridazine 2-oxide (**120**) gave the corresponding acetate (**121**) which has been hydrolyzed to 3-hydroxymethyl-6-methoxypyridazine (**122**)<sup>630, 633</sup> and then oxidized to the known 6-oxo-1,6-dihydro-3-pyridazinecarboxylic acid (**123**).<sup>630</sup> Similarly, 6-acetoxymethyl-3-phenylpyridazine is obtained from 6-methyl-3-phenylpyridazine 1-oxide<sup>665, 628</sup> and 3-ethoxy-6-hydroxymethylpyridazine from 3-ethoxy-6-methylpyridazine 1-oxide.<sup>628</sup>

If the ortho position in pyridazine *N*-oxides is substituted by other than a methyl group, and if the para position relative to the *N*-oxide is substituted by methyl, then rearrangement may proceed to the 4-methyl group, but usually by-products are formed. An example of such a rearrangement is 3,6-dimethoxy-4-methylpyridazine 1-oxide which forms the expected 4-acetoxymethyl-3,6-dimethoxypyridazine

<sup>665</sup> M. Kumagai, *Nippon Kagaku Zasshi* **81**, 350 (1960); *Chem. Abstr.* **55**, 6485 (1961).

along with 1-hydroxy-3-methoxy-4-methyl-6(1*H*)-pyridazinone.<sup>571</sup> A mixture, consisting of 4-hydroxymethyl- (8%), 4-chloromethyl- (11%), and 6-chloro-3,4-dimethylpyridazine (1%), resulted from treatment of 6-chloro-3-methoxy-4-methylpyridazine 1-oxide with acetic anhydride.<sup>571</sup> Other pyridazine *N*-oxides, such as 3-methylpyridazine 1- or 2-oxide and 6-chloro-3-methylpyridazine 2-oxide, have been found to be resistant to such rearrangements.<sup>630</sup>

1-Acetoxy-3-methoxy-6(1*H*)-pyridazinone and 1,3-dimethoxy-6(1*H*)-pyridazinone are formed by the reaction of 3,6-dimethoxy-pyridazine 1-oxide with acetic anhydride. In addition, 1,3-dimethoxy-6(1*H*)-pyridazinone is obtained from the last-mentioned starting



compound by merely heating it. In *N*-oxides with ortho alkoxy groups (124), the alkyl group may migrate to the *N*-oxide grouping (125) on heating with *p*-toluenesulfonic acid. Examples of this rearrangement are: 3,6-dimethoxypyridazine 1-oxide to 1,3-dimethoxy-6(1*H*)-pyridazinone; 3,6-dimethoxy-4-methylpyridazine 1-oxide to 1,3-dimethoxy-4-methyl-6(1*H*)-pyridazinone; and 3,6-dimethoxy-5-methylpyridazine 1-oxide to 1,3-dimethoxy-5-methyl-6(1*H*)-pyridazinone.<sup>642</sup>

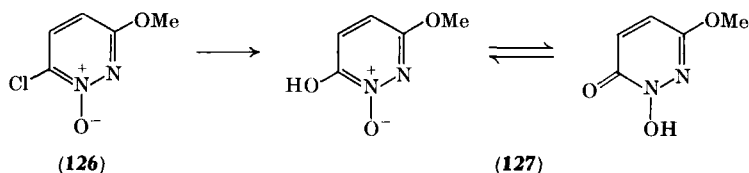
Analogous reactions are known also with 4-(or 5-)methoxypyridazine 1-oxides. Examples are the formation of 1-methoxy-(or ethoxy)-4(1*H*)-pyridazinone (together with 4-hydroxypyridazine 1-oxide) from 4-methoxy(or ethoxy)pyridazine 1-oxide and 1,3,4-trimethoxy-6(1*H*)-pyridazinone from 3,4,6-trimethoxypyridazine 1-oxide,<sup>568</sup> while 5-methoxypyridazine 1-oxide gave exclusively 2-methyl-3(2*H*)-pyridazinone 1-oxide.<sup>642</sup>

*N* → *ortho* rearrangement of the heterocyclic aryl group, which occurs in concentrated sulfuric acid at 0° with simultaneous loss of carbon dioxide in 2-anilino-carbonyl quinoxaline *N*-oxides, does not occur with the corresponding pyridazine *N*-oxides.<sup>666</sup>

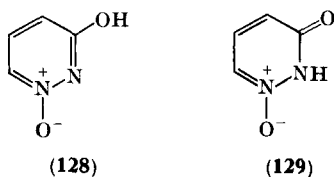
<sup>666</sup> M. S. Habib and C. W. Rees, *J. Chem. Soc.*, 3371 (1960).

*e. Hydrolysis of Pyridazine N-Oxides.* The acetamido group in 3-acetamidopyridazine 2-oxides is hydrolyzed normally to yield the corresponding 3-aminopyridazine 2-oxides.<sup>440, 625, 649</sup>

Hydrolysis of 3-chloropyridazine 1-oxide with dilute sodium hydroxide solution gives 3-hydroxypyridazine 1-oxide<sup>645</sup> (identical with that synthesized by another method<sup>637</sup>) and likewise 6-chloro-3-methoxypyridazine 1-oxide (**126**) with acetic acid and sodium acetate yields 3-methoxy-6-hydroxypyridazine 1-oxide or its tautomeric form, i.e., 1-hydroxy-3-methoxy-6(1*H*)-pyridazinone (**127**).<sup>629, 639</sup>



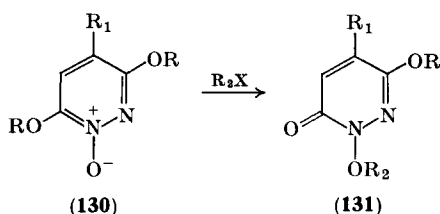
Compound **127** exists in the 1-hydroxy-3-methoxy-6(1*H*)-pyridazinone form, on the basis of UV and IR data.<sup>639</sup> By contrast, 6-chloro-3-methoxypyridazine 1-oxide when heated with 5% sodium hydroxide afforded 6-chloro-3(2*H*)-pyridazinone 1-oxide.<sup>656</sup>



Removal of alkoxy groups from 3-(4-, 5-, or 6-)alkoxypyridazine 1-oxides in alkaline medium produces the corresponding hydroxypyridazine 1-oxides.<sup>456, 539, 545, 627, 637</sup> On the basis of UV spectra and pK values for 3-hydroxypyridazine 1-oxides it is postulated that there is a larger contribution of the phenolic structure (**128**) than of the tautomeric pyridazinone *N*-oxide structure (**129**).<sup>637</sup>

3,6-Dimethoxypyridazine 1-oxide and its 4-chloro and 4-methoxy analogs are hydrolyzed with sodium methoxide or hydrazine hydrate to 1-hydroxy-3-methoxy-6(1*H*)-pyridazinone and its 4-chloro and 4-methoxy analogs.<sup>568</sup>

*f. Miscellaneous Reactions.* Alkylations and acylations of pyridazine *N*-oxides are important from the synthetic and the structural point of view. Many pyridazinone derivatives (**131**) have been synthesized from 3,6-dialkoxy-4-substituted pyridazine 1-oxides (**130**) with the aid of alkylating or acylating agents.<sup>667</sup> In **131** R may stand for an alkyl group, R<sub>1</sub> represents hydrogen or an alkyl group, and R<sub>2</sub> may be an alkyl, acyl, or acylated alkyl group. 1-Phenacyloxy-3-alkoxy-6(1*H*)-pyridazinones are decomposed by heat, alcohol, acid, or



alkali and 3-alkoxy-6(1*H*)-pyridazinones and phenylglyoxal are formed.<sup>667</sup>

If 3,6-dichloropyridazine 1-oxide or 6-chloro-3-methoxypyridazine 1-oxide are heated with acetic anhydride, 1-acetoxy-3-chloro-6(1*H*)-pyridazinone or its 3-methoxy analog are formed.<sup>647</sup> Upon hydrolysis the corresponding 1-hydroxy compounds are obtained. Likewise, 3,6-dimethoxy-4-nitropyridazine 1-oxide reacts with acetyl or benzoyl chloride to give 1-acetoxy-(or benzyloxy)-4-chloro-3-methoxy-6(1*H*)-pyridazinone, the displacement of the nitro group by chlorine taking place simultaneously. It has been established that in this reaction 3,6-dimethoxy-4-chloropyridazine 1-oxide is formed as an intermediate which reacts further with acetyl chloride to give the foregoing acetoxy derivative.<sup>643</sup>

Acylation or alkylation of 1-hydroxypyridazinones, as exemplified by benzylation of 1-hydroxy-3-methoxy-6(1*H*)-pyridazinone and its 4- or 5-substituted derivatives<sup>456, 658</sup> or methylation of 1-hydroxy-3,4-disubstituted-6(1*H*)-pyridazinones,<sup>568</sup> affords the corresponding 1-benzyloxy and 1-methoxy derivatives, respectively.

Methylation of 3-methyl-6(1*H*)-pyridazinone 2-oxide and its 4-methyl analog with dimethyl sulfate produced mixtures of 1,3-dimethyl-6(1*H*)-pyridazinone 2-oxide and 3-methyl-6-methoxypyridazine 2-oxide (by-product) or of 3,4-dimethyl-6-methoxypyridazine

<sup>667</sup> M. Yanai, T. Kinoshita, and M. Yamaguchi, *Yakugaku Zasshi* **86**, 81 (1966).

2-oxide and 1,3,4-trimethyl-6(1*H*)-pyridazinone 2-oxide, separable on the basis of different basicity.<sup>632</sup> By contrast, methylation with methyl iodide in the presence of silver oxide gives only one product. Thus, 3-methyl-6(1*H*)-pyridazinone 2-oxide yields 3-methyl-6-methoxypyridazine 2-oxide,<sup>634</sup> and 1-hydroxy-3-methoxy-4-(or 5)-substituted-6(1*H*)-pyridazinones form 1,3-dimethoxy-4-(or 5)-substituted-6(1*H*)-pyridazinones.<sup>456, 639</sup> A similar reaction course is observed when benzylation is performed in the presence of sodium methoxide.<sup>639</sup>

Methylation with methyl iodide proceeds normally with 3,6-dimethyl-5-hydroxypyridazine 1-oxide to give the corresponding 5-methoxy derivative, although in low yield, whereas from 4-hydroxypyridazine 1-oxide and its 3,6-dimethyl analog the corresponding 1-methoxy-4(1*H*)-pyridazinones were obtained.<sup>539, 627</sup>

It has been reported that the reaction between 6-methyl-4-nitropyridazine 1-oxide or its 3-substituted derivatives (**132**)<sup>624, 664</sup> and acetyl chloride gives the corresponding 4-chloro-6-methylpyridazine 1-oxides (**133**) along with a high melting product, identified later as 4-chloro-6-formylpyridazine 1-oxide oxime (**134**). The latter can be converted via the monoacetate (**135**) into the nitrile *N*-oxide (**136**) or with phosphorus oxychloride into the nitrile (**137**).<sup>664</sup> Acetyl nitrite is probably formed and this nitrosates the reactive methyl group. However, this mechanism is not proved.

To ascertain the structure of the above aldoximes, various substituted pyridazine *N*-oxides have been treated with amyl nitrite and sodium amide in liquid ammonia. The products were the unstable  $\alpha$ - or syn-aldoximes, which are readily isomerized to the stable  $\beta$  or anti isomers under the influence of heat or hydrochloric acid.<sup>668</sup>

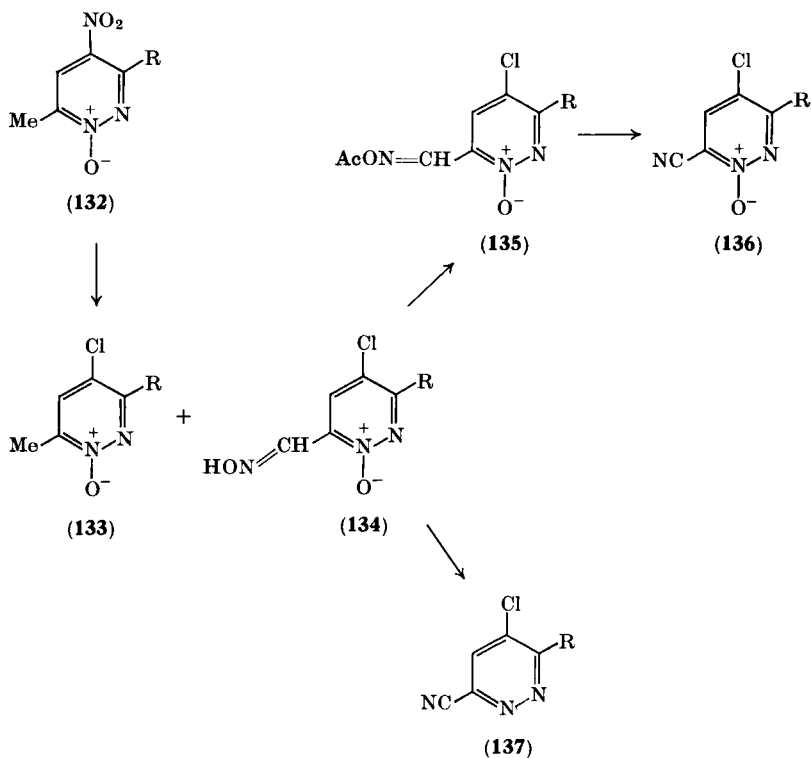
Amino-substituted pyridazine *N*-oxides react normally to give with acetic anhydride the acetamido derivatives.<sup>649, 651</sup>

Like 3- and/or 6-methylpyridazines, their *N*-oxide counterparts condense with aromatic aldehydes. Thus, 3,6-dimethylpyridazine 1-oxide always gives 3,6-distyrylpyridazine 1-oxides, regardless of the ratio of reactants.<sup>669</sup> The reactivity of the 3- and 6-methyl groups is similar. From the reactions of 3-, 4-, 5-, and 6-methylpyridazine 1-oxides with benzaldehyde<sup>669</sup> it is inferred that methyl groups at positions 4 and 6 exhibit about the same order of reactivity, whereas

<sup>668</sup> M. Ogata, *Chem. Pharm. Bull. (Tokyo)* **11**, 1517 (1963).

<sup>669</sup> T. Itai, S. Sako, and G. Okusa, *Chem. Pharm. Bull. (Tokyo)* **11**, 1146 (1963).

the 5-methyl group is more and the 3-methyl group less reactive compared to the 4- or 6-methyl groups. When condensations of 4-, 5-, or 6-methylpyridazine 1-oxide with benzaldehyde are carried out at 40° the corresponding  $\beta$ -(hydroxyphenethyl)pyridazine 1-oxides were isolated which can be dehydrated by heating in methanolic

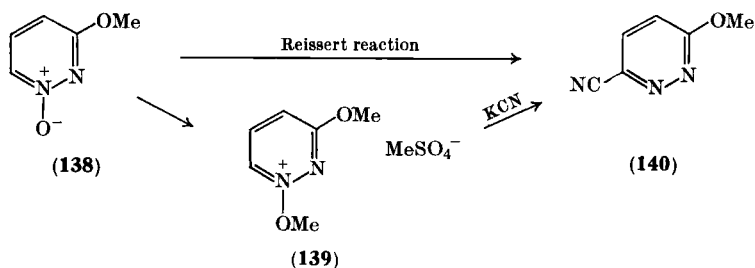


sodium methoxide to the styryl derivatives.<sup>669</sup> These and the bis-styryl derivatives exist in the trans form and the side chain double bond can be catalytically hydrogenated.<sup>669</sup>

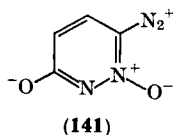
3-Methoxypyridazine 1-oxide (138) when treated with dimethyl sulfate gives the methosulfate (139); this is transformed by potassium cyanide into 3-methoxy-6-cyanopyridazine (140), which can in turn be obtained directly from 138 by the Reissert reaction.<sup>670</sup>

<sup>670</sup> H. Igeta, *Chem. Pharm. Bull. (Tokyo)* **11**, 1472 (1963).

There are several other reactions pertinent to functional groups present in pyridazine *N*-oxides. The cyano group of 6-cyano-3-methylpyridazine 1-oxide is normally hydrolyzed to the carboxyl in concentrated sulfuric acid, whereas heating 5-chloro-6-cyano-3-methylpyridazine 1-oxide with 2 equivalents of sodium methoxide in a sealed tube gave 6-carbamoyl-5-hydroxy-3-methylpyridazine



1-oxide.<sup>658</sup> Hydrazinopyridazine *N*-oxides form normal hydrazones and thiosemicarbazides<sup>452, 564</sup> and can be transformed into azidopyridazine *N*-oxides.<sup>452, 564</sup> From the reaction between diphenylpicrylhydrazyl and 3-azidopyridazine 1- or 2-oxide it is concluded that the 3-azido group in 2-oxide is more reactive than that of the isomeric 1-oxide.<sup>564</sup> If 3-azidopyridazine 1-oxide is refluxed in xylene, 3,3'-azodipyridazine-1,1'-dioxide is formed.<sup>564</sup> 4- and 5-azidopyridazine 1-oxides were prepared from the corresponding hydrazino compounds under the action of nitrous acid.<sup>452</sup>



3-Amino-6-chloropyridazine 2-oxide can be diazotized to give anhydro 3-diazo-6-hydroxypyridazine diazonium hydroxide 2-oxide (141); the structure is supported by infrared spectrum and conversion into 3-hydroxypyridazine 1-oxide on refluxing in methanol.<sup>625, 649</sup> When coupled with 2-naphthol in alkaline medium, the diazonium compound gives a purple dye.<sup>649</sup>

## H. REDUCED PYRIDAZINES

According to the number and position of hydrogen atoms in the pyridazine nucleus several reduced pyridazines are theoretically possible and existence of most of them has been registered. Frequently, the structures of reduced pyridazines are written as proposed by the authors, but a detailed study relating their structures is lacking.

1. *Dihydropyridazines*

Of the six theoretically possible dihydropyridazine derivatives only three isomers are known: the 1,2-, 1,4-, and 4,5-dihydropyridazines. As with pyridines, it is expected that those dihydropyridazines with structures containing  $\text{—N=N—}$  bonds will be less stable.

1,2-Dihydropyridazines have not been prepared by direct cyclizations; reductions of pyridazines and oxidations of reduced pyridazines are known. 3,6-Diphenylpyridazine is reduced with sodium and ethanol<sup>671</sup> to the 1,2-dihydro derivative and the 1,2-dicarbethoxy analog is formed in a selenium dioxide oxidation of the corresponding 1,2,3,6-tetrahydro compound.<sup>321</sup> 1-Carbethoxy- or 1,2-dicarbethoxy-1,2-dihydropyridazine was obtained similarly from an alkali treatment of 1,2-dicarbethoxyhexahydropyridazine.<sup>672</sup> 1,2-Dihydro-3,6-diphenylpyridazine is unstable and oxidizes to the parent pyridazine in the presence of air or on attempted acetylation.<sup>673</sup>

1,4-Dihydropyridazines are obtained from 1,4-dicarbonyl compounds and hydrazine (Section III, B) or from the reaction of sym-tetrazines and simple ethylenic compounds (Section III, H). There are also a few special reactions, such as that between a tetrahydrofuran and phenylhydrazine,<sup>348</sup> or from a 1,4,5,6-tetrahydropyridazine derivative.<sup>16</sup> The 1,4-dihydro structure has been found to be correct, rather than the 1,6-dihydro structure, postulated earlier for some of these reduced pyridazines (Section III, H). 1,4-Dihydropyridazines can be reduced or oxidized easily and acid treatment of 1-tosyl-1,4-dihydropyridazine causes rearrangement to 1-tosylaminopyrrole.<sup>16</sup>

4,5-Dihydropyridazines result from the addition of Grignard reagents to 3,6-disubstituted pyridazines (Section IV, A) or from

<sup>671</sup> G. Rosseels, *Ingr. Chimiste* **46**, 7 (1964).

<sup>672</sup> M. Rink, S. Mehta, and K. Grabowski, *Arch. Pharm.* **292**, 225 (1959).

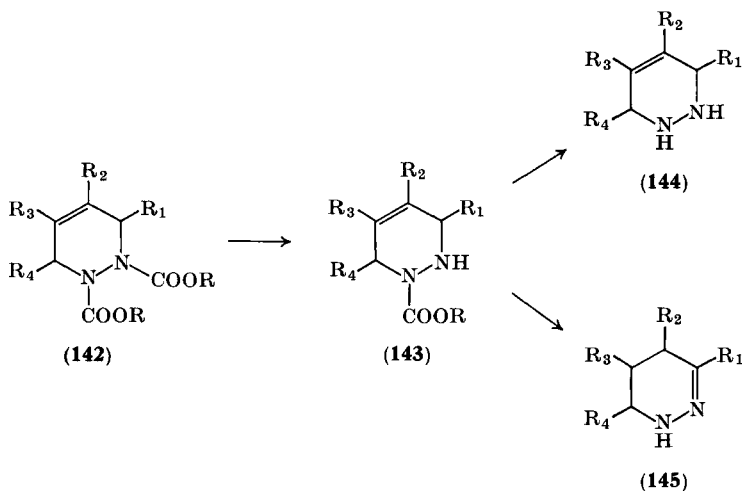
<sup>673</sup> G. Rosseels, *Ingr. Chimiste* **42**, 285 (1960).



some 1,4-dicarbonyl compounds and hydrazines (Section III, B). The stability depends on substituents in the pyridazine nucleus. An anthracenodiphenyl-4,5-dihydropyridazine is unstable and decomposes spontaneously into 3,6-diphenylpyridazine,<sup>407</sup> but some 4,5-dihydropyridazines, obtained in the Grignard reaction, are resistant to catalytic dehydrogenation<sup>412, 413</sup> or even to bromine and acetyl peroxide,<sup>412</sup> although in other cases bromine caused dehydrogenation.<sup>413</sup> 3,6-Diphenyl-4,5-dihydropyridazine is more stable than the isomeric 1,2-dihydro compound, since this is isomerized under the influence of alkalis to the 4,5-dihydro compound.<sup>321</sup>

## 2. Tetrahydropyridazines

Of the four possible tetrahydropyridazines representatives of only three isomers are known; 1,2,3,4-tetrahydropyridazines have not been described.



1,2,3,6-Tetrahydropyridazines are formed in the Diels-Alder reaction between a diene and an azo compound (Section III, F) and most of the adducts carry a carbalkoxy group at positions 1 and 2. Partial alkaline hydrolysis with subsequent decarboxylation converts these compounds (142) in the *N*-monosubstituted derivatives (143),<sup>327</sup>

<sup>674</sup> which can be further hydrolyzed and decarboxylated to 1,2,3,6-tetrahydropyridazines unsubstituted at positions 1 and 2 (**145**). Structure **144** has been proposed for 1,2,3,6-tetrahydropyridazine itself and some its alkyl or aryl analogs on the basis of formation of dibenzoyl derivatives,<sup>330, 675-677</sup> condensations with  $\alpha$ -phenylbenzoyl-acetate,<sup>333</sup> succinyl dichloride,<sup>678</sup> malonyl chloride,<sup>678a</sup> or phthalic anhydride,<sup>676</sup> since polycyclic systems were formed involving the reactions on both NH groups, and by analogy.<sup>326</sup> Similarly, evidence for the presence of a secondary amino group in **143** derives from reactions with phenyl isothiocyanate to form thiourea derivatives.<sup>330, 674, 679</sup>

However, removal of the second carbethoxy or acyl group from **143** has been in many cases formulated as to proceed with a migration of the double bond to give compounds of structure **145**, i.e., 1,4,5,6-tetrahydropyridazines.<sup>249, 321, 324, 327, 334, 335, 680-682</sup> Also a reinvestigation of the structure of 3,6-diphenyl-1,2,3,6-tetrahydropyridazine<sup>330, 331</sup> revealed on the basis of chemical transformations that the structure of a 1,4,5,6-tetrahydropyridazine (**145**,  $R_1 = R_4 = \text{Ph}$ ,  $R_2 = R_3 = \text{H}$ ) is more probable.<sup>321</sup>

Well-defined isomeric tetrahydropyridazines of the **144** and **145** type exist with different physicochemical characteristics, but for others definitive structure assignment is required.

<sup>674</sup> R. Ya. Levina, Yu. S. Shabarov, and M. G. Kuz'min, *Zh. Obshch. Khim.* **30**, 2469 (1960).

<sup>675</sup> R. Ya. Levina, Yu. S. Shabarov, and M. G. Kuz'min, *Dokl. Akad. Nauk SSSR* **127**, 111 (1959).

<sup>676</sup> R. A. Clement, *J. Org. Chem.* **25**, 1724 (1960).

<sup>677</sup> Yu. S. Shabarov, M. G. Kuz'min, and R. Ya. Levina, *Zh. Obshch. Khim.* **30**, 2473 (1960).

<sup>678</sup> I. Zugravescu and E. Carp, *Analele Stiint. Univ. "Al. I. Cuza," Iasi, Sect. Ic: Chem.* **11**, 59 (1965); *Chem. Abstr.* **63**, 14855 (1965).

<sup>678a</sup> I. Molnar and T. Wagner-Jauregg, *Pharm. Acta Helv.* **39**, 155 (1964).

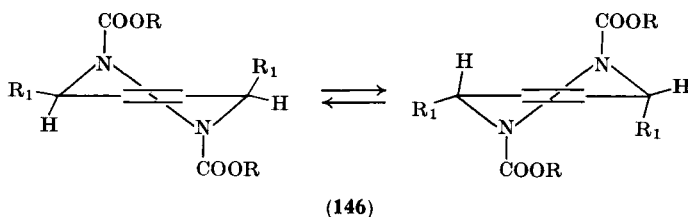
<sup>679</sup> Yu. S. Shabarov, A. P. Smirnova, and R. Ya. Levina, *Zh. Obshch. Khim.* **34**, 390 (1964).

<sup>680</sup> Yu. S. Shabarov, R. Ya. Levina, M. G. Kuz'min, N. I. Vasil'ev, and N. A. Damir, *Zh. Obshch. Khim.* **30**, 3210 (1960).

<sup>681</sup> Yu. S. Shabarov, N. I. Vasil'ev, and R. Ya. Levina, *Zh. Obshch. Khim.* **31**, 2482 (1961).

<sup>682</sup> R. Ya. Levina, M. G. Kuz'min, and Yu. S. Shabarov, *Vestn. Mosk. Univ., Ser. Mat., Mekhan., Astron., Fiz. i Khim.* **12**, 170 (1957); *Chem. Abstr.* **52**, 391 (1958).

The conformation of 1,2,3,6-tetrahydropyridazines<sup>683-688</sup> and some hexahydropyridazines<sup>685, 687</sup> has been studied by NMR spectroscopy. In conformational changes both ring inversion (146) and hindered rotation about N—COOR bonds are involved.<sup>687</sup> Unusually high-energy barriers (18.9–21.4 kcal/mole) were found for ring inversion for these six-membered ring systems<sup>687, 689</sup> which appear to be associated with interactions between the adjacent *N*-acyl substituents.<sup>687</sup> Signals for this structure (146, R<sub>1</sub> = Me) were



assigned as  $\tau_{H_6} = 4.0$ ,  $\tau_{H_5} = 3.70$ ,  $\tau_{H_4} = 4.28$ ,  $\tau_{H_3} = 4.75$ ;  $J_{5,6} = 5.0$  and  $J_{3,4} = 2.0$  cps.<sup>688</sup> The related 1,2-dimethyl-1,2,3,6-tetrahydropyridazines and the hexahydro analogs behave similarly and the NMR spectra exhibit increased structure at low temperatures due to ring and nitrogen inversion.<sup>689a</sup> The energy barriers are for 6–7 kcal/mole lower than those of the corresponding N—COOMe analogs.

1,2,3,6-Tetrahydropyridazines are oxidized to pyridazines by means of bromine.<sup>326, 330</sup> Addition of hydrogen,<sup>249, 321, 322, 328, 330, 332, 336, 672, 677, 690–693</sup> bromine,<sup>690</sup> or mercuric acetate<sup>325</sup> at the double bond

<sup>683</sup> C. H. Bushweller, *Chem. Commun.*, 80 (1966).

<sup>684</sup> R. Daniels and K. A. Roseman, *Chem. Commun.*, 429 (1966).

<sup>685</sup> W. Koch and H. Zollinger, *Helv. Chim. Acta* **46**, 2697 (1963).

<sup>686</sup> B. J. Price, R. V. Smallman, and I. O. Sutherland, *Chem. Commun.*, 319 (1966).

<sup>687</sup> B. J. Price, I. O. Sutherland, and F. G. Williamson, *Tetrahedron* **22**, 3477 (1966).

<sup>688</sup> B. H. Korsch and N. V. Riggs, *Tetrahedron Letters*, 5897 (1966).

<sup>689</sup> J. C. Brelrier and J. M. Lehn, *Chem. Commun.*, 426 (1965).

<sup>689a</sup> J. E. Anderson and J. M. Lehn, *Bull. Chem. Soc. France*, 2402 (1966).

<sup>690</sup> M. Rink and K. Grabowski, *Naturwissenschaften* **43**, 326 (1956).

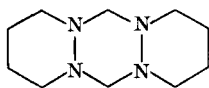
<sup>691</sup> Yu. S. Shabarov, N. I. Vasil'ev, N. K. Mamaeva, and R. Ya. Levina, *Zh. Obshch. Khim.* **33**, 1206 (1963).

<sup>692</sup> I. Molnar, *Helv. Chim. Acta* **49**, 586 (1966).

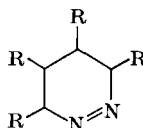
<sup>693</sup> C. G. Overberger and G. Kesslin, *J. Org. Chem.* **27**, 3898 (1962).

has been achieved. 1,2,3,6-Tetrahydropyridazine with bromine gives 1,2,3,4-tetrabromobutane,<sup>672</sup> or simply adds bromine.<sup>332</sup> Reduction of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine by lithium aluminum hydride afforded 1,2-dimethylhexahydropyridazine as the major product together with a small quantity of the polycycle (147), obtainable also by other routes.<sup>694</sup>

Besides the above-mentioned method of obtaining 1,4,5,6-tetrahydropyridazines, these may be prepared from 4,5-dihydro-3(2*H*)-pyridazinones, which are formed from 1,4-ketoacids and hydrazines.



(147)



(148)

Partial reduction of the oxo group can be accomplished with lithium aluminum hydride<sup>691, 695–697</sup> to give 145. Similarly, hexahydropyridazines are dehydrogenated with mercuric oxide, hydrogen peroxide, or cupric chloride–ammonia<sup>328, 332, 675, 677</sup> to 1,4,5,6-tetrahydropyridazines. The reaction with mercuric oxide may involve first the formation of a 3,4,5,6-tetrahydropyridazine (148), as the 3,6-dimethyl analog is slowly isomerized to 3,6-dimethyl-1,4,5,6-tetrahydropyridazine when stored at  $-20^{\circ}$ ,<sup>328</sup> and the diphenyl analog isomerizes rapidly.<sup>249</sup>

1,4,5,6-Tetrahydropyridazines with unsubstituted NH groups behave as secondary amines; the double bond has been hydrogenated with lithium aluminum hydride<sup>336, 691</sup> and addition of hydrogen cyanide is known.<sup>698</sup> Oxidation of 3,6-diphenyl-1,4,5,6-tetrahydropyridazine with lead dioxide results in aromatization.<sup>321</sup>

1,4,5,6-Tetrahydropyridazines decompose under the catalytic influence of platinum and in the presence of alkali at temperatures above  $200^{\circ}$  into cyclobutanes (151) along with other decomposition

<sup>694</sup> M. Rink and S. Mehta, *Naturwissenschaften* **45**, 313 (1958).

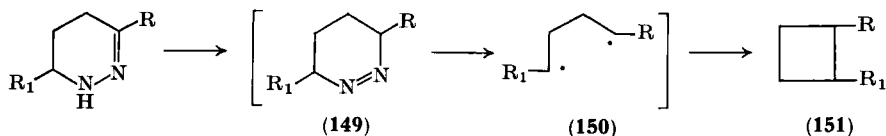
<sup>695</sup> Yu. S. Shabarov, N. I. Vasil'ev, N. K. Mamaeva, and R. Ya. Levina, *Dokl. Akad. Nauk SSSR* **135**, 879 (1960).

<sup>696</sup> F. J. Marshall, *J. Am. Chem. Soc.* **78**, 3696 (1956).

<sup>697</sup> S. Wawzonek and R. C. Gueldner, *J. Org. Chem.* **30**, 3031 (1965).

<sup>698</sup> C. G. Overberger and N. R. Byrd, *J. Org. Chem.* **27**, 1568 (1962).

products such as alkenes, nitrogen, etc.<sup>324, 327, 335, 680–682, 693, 695</sup> The reaction is formulated as a decomposition of the intermediate 3,4,5,6-tetrahydropyridazine (149) into a free radical (150) and subsequent



cyclization. However, 3-(*p*-hydroxy or *p*-aminophenyl)-1,4,5,6-tetrahydropyridazines are preferentially dehydrogenated at temperatures of about 400° and the corresponding pyridazines are formed.<sup>681</sup>

### 3. Hexahydropyridazines

Hexahydropyridazines are usually prepared by hydrogenation of the double bond of the readily accessible 1,2,3,6-tetrahydropyridazines. Hexahydropyridazine is obtained from 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine by hydrogenation and subsequent hydrolysis and concurrent decarboxylation.<sup>321, 330, 672, 690</sup> The same method has been applied for the synthesis of its 3-methyl,<sup>677</sup> 4-methyl,<sup>330</sup> 3,6-dimethyl,<sup>328</sup> 4,5-dimethyl,<sup>332</sup> or 3-phenyl analogs.<sup>691</sup> The same procedure, when applied to the synthesis of 3,6-diphenylhexahydropyridazine gave instead 3,6-diphenyl-3,4,5,6-tetrahydropyridazine on account of autoxidation during concentration of the ether extract. The product is then readily isomerized to 3,6-diphenyl-1,4,5,6-tetrahydropyridazine by heat or under the influence of polar solvents.<sup>322</sup> 3,6-Diphenyl-3,4,5,6-tetrahydropyridazine has been also considered to result from a direct cyclization,<sup>390</sup> but it was later shown on the basis of ultraviolet spectroscopic evidence and chemical properties to possess the isomeric 1,4,5,6-tetrahydro structure.<sup>249</sup>

Alternatively, hexahydropyridazines are formed when reducing the double bond of tetrahydropyridazines catalytically<sup>321, 322, 330, 332, 336, 697</sup> or with lithium aluminum hydride.<sup>691</sup> A particular case presents the reduction of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine with lithium aluminum hydride giving as the major product 1,2-dimethylhexahydropyridazine, with a small amount of the tricyclic product (147).<sup>336</sup>

Reduction with sodium and ethanol has been used in the synthesis of hexahydropyridazine<sup>14</sup> which is obtained together with 1,4-diaminobutane. Similarly, reduction of 3-(*p*-tolyl)-pyridazine gave besides the corresponding hexahydropyridazine also a substituted pyrrolidine.<sup>154</sup> 3,6-Dimethylpyridazine, when reduced in this way, can give its dihydro<sup>226, 244</sup> or hexahydro analog.<sup>239</sup> In all other cases of pyridazine reductions, no dihydro- and tetrahydropyridazines have been isolated, probably on account of their more ready reducibility compared to aromatic pyridazines.

Hexahydropyridazines result also from the reaction between butadienedioxide and hydrazines<sup>699</sup> or from other aliphatic components.<sup>377, 378, 531</sup>

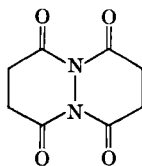
The structure of hexahydropyridazines has been investigated with NMR spectroscopy. The NMR spectra of 1,2-diacetyl-*cis*-4,5-hexahydropyridazine derivatives were analyzed in terms of an  $A_2B_2X_2$  system resulting from the ring protons with coupling constants  $J_{AX'}$ ,  $J_{BX'}$ ,  $J_{A'X'}$ , and  $J_{B'X'}$  compatible with the dihedral angles of the chair conformation. At the same time two distinct types of ring methyl group and acetyl methyl group are observed. The low intensity of the acetyl methyl signals suggests that, besides an inflexible chair conformation, other conformational types are present in low concentration.<sup>687</sup> The higher-energy barrier to rotation about the N—COOEt bond in hexahydropyridazine derivatives<sup>687</sup> as compared to tetrahydropyridazines,<sup>686, 687, 689</sup> which are comparable with energies determined for ring inversion in tetrahydropyridazines,<sup>687, 689</sup> makes it difficult to characterize the type of conformational change taking place because of the magnitude of the energy barrier involved. The NMR studies of *trans*-3,4-dihydroxyhexahydropyridazines led to the conclusion that these compounds exist in such a conformation that all substituents are axial in the chair form.<sup>685</sup> It is hoped that further study of conformations other than the chair will provide more convincing evidence as regards the fine structure of such compounds.

Like other reduced pyridazines, hexahydropyridazines can be oxidized to pyridazines and acylated, and they form thiourea derivatives with isothiocyanates. Hexahydropyridazine condenses with 1,4-dihalobutanes to give the diazadecalin<sup>678, 690, 694</sup>; with formaldehyde or benzaldehyde, **147** or its diphenyl analog have been obtained.<sup>694</sup>

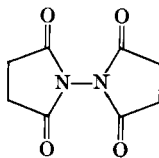
<sup>699</sup> H. R. Meyer and R. Gabler, *Helv. Chim. Acta* **46**, 2685 (1963).

#### 4. Reduced Pyridazinones

Derivatives of 3(2*H*)-pyridazinone are stable to acids, but those of 4,5-dihydro-3(2*H*)-pyridazinones, readily accessible from 1,4-keto-acids and hydrazines, are labile to acids, alkalis, and chlorine.<sup>699a</sup> Decomposition results in the formation of substituted butyric acids<sup>108, 123, 129, 135, 145, 146, 162</sup> and the acid lability of 5-substituted 3-methyl analogs was used to prepare  $\alpha$ -alkyl-substituted levulinic acids,<sup>124, 125</sup> whereas under the influence of alkali  $\beta$ -acylpropionic acids are obtained.<sup>406</sup> 1-Aryl-4,5-dihydro-3(2*H*)-pyridazinones are also split by acids and a simultaneous rearrangement to indole derivatives (Section IV, I) takes place.



(152)



(153)

The presence of reactive hydrogens at position 4 is revealed from the interaction of 4,5-dihydro-3(2*H*)-pyridazinones with aldehydes and the corresponding 4-arylidene derivatives were readily prepared.<sup>414</sup> Condensation with diethyl oxalate has also been performed<sup>138</sup> and *p*-nitrosodialkylanilines gave the corresponding azomethines in the presence of an alkoxide.<sup>700</sup> 2-Substituted 4,5-dihydro-3(2*H*)-pyridazinones do not undergo a Mannich reaction at the reactive 4-position, but the 2-unsubstituted analogs yield the corresponding 2-Mannich bases.<sup>414</sup> Similarly, Michael-type additions, such as cyanoethylation, proceed on the ring nitrogen yielding the 2-cyanoethylated products.<sup>414</sup>

The reactivity and chemistry of tetrahydro-3,6-pyridazinediones has not been much investigated. The parent compound (cyclic succinhydrazide) has been obtained by aluminum amalgam reduction of maleic hydrazide.<sup>301, 302</sup> Attempts to prepare it by alternative methods were unsuccessful (Section III, D). It forms a *N,N*-dimethyl or diacetyl and a *N*-monoethyl derivative; with benzenesulfonyl

<sup>699a</sup> W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 3508 (1950).

<sup>700</sup> E. Bulka and H. Gille, *Z. Chem.* **5**, 374 (1965).

chloride a mixture of the monobenzenesulfonyl derivative and **152**, which was at first thought to be **153**, has been obtained, and with hydrazine hydrate it is readily converted at room temperature into succindihydrazide. Authentic **152** is formed when reacting the cyclic succinhydrazide with succinoyl chloride in toluene,<sup>701</sup> but the same reaction in dioxan or when refluxing **152** in dioxan causes the formation of the more stable *N,N'*-bisuccinimidyl (**153**). This compound had been obtained earlier.<sup>301, 702</sup> but was assigned structure **152**.

In contrast to maleic hydrazide which gives only *N*-substituted monoadducts in the Michael-type addition reactions, cyclic succinhydrazide can give mono and diaddition products.<sup>531</sup>

1,2-Disubstituted tetrahydro-3,6-pyridazinediones are obtained by catalytic hydrogenation of their aromatic counterparts,<sup>288, 291</sup> but maleic hydrazide itself is reported to be resistant to hydrogenation.<sup>703</sup> 1,2-Disubstituted tetrahydro-3,6-pyridazinediones react at elevated temperatures with amines or alkalis and the ring is broken at the  $N_1-C_6$  bond.<sup>288</sup> With hydrazine, however, the corresponding succindihydrazide and a disubstituted hydrazine are obtained.<sup>288</sup>

## I. RING REARRANGEMENTS OF PYRIDAZINES

Some interesting ring contractions from pyridazine derivatives to pyrazolone, pyrrole, or indole derivatives are known.

Formation of pyrazoles from pyridazines was first observed by Ach in 1889<sup>107</sup>; he obtained 1-phenyl-3-methylpyrazole-5-carboxylic acid from acid treatment of 4-hydroxy-6-methyl-2-phenyl-3(2*H*)-pyridazinone or the 4-ethoxy analog. Recently, 4-hydroxy-5-nitro-3(2*H*)-pyridazinones have been found to rearrange likewise into 4-nitropyrazole-5-carboxylic acids. Ring nitrogen-unsubstituted or 2-alkyl-substituted 4-hydroxy-5-nitro-3(2*H*)-pyridazinones (**154**, R = H or alkyl) rearrange only under the influence of acids with simultaneous decarboxylation to **156**, whereas the 2-arylated derivatives (**154**, R = Ar) rearrange in alkaline medium to acids (**155**).<sup>3</sup> Other 4-hydroxy-3(2*H*)-pyridazinones with a hydroxyl group, or with other groups

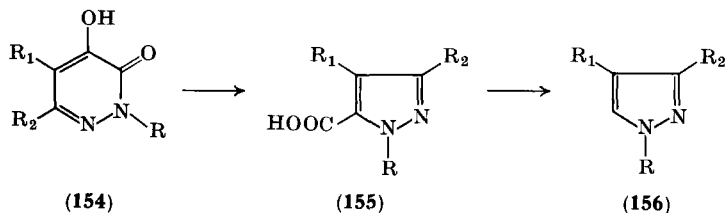
<sup>701</sup> E. Hedaya, R. L. Hinman, and S. Theodoropulos, *J. Am. Chem. Soc.* **85**, 3052 (1963).

<sup>702</sup> H. Feuer and J. E. Wyman, *Chem. & Ind. (London)*, 577 (1956).

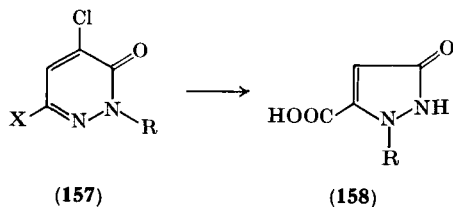
<sup>703</sup> C. Ainsworth, *J. Am. Chem. Soc.* **78**, 1636 (1956).



which under the influence of alkali are readily replaced by hydroxyl, at position 5 or 6, readily undergo ring contraction into 5-(or 3-)pyrazolones when heated in the presence of alkalis. Examples of such rearrangements include the formation of 1-phenyl-2-methyl-5-pyrazolone-3-carboxylic acid from 1-phenyl-2-methyl-4-hydroxy-1,2,3,6-tetrahydropyridazine-3,6-dione<sup>467</sup> and 1-phenyl-5-pyrazolone-4-carboxylic acid from the corresponding 5-diazopyridazone (97).<sup>3</sup>



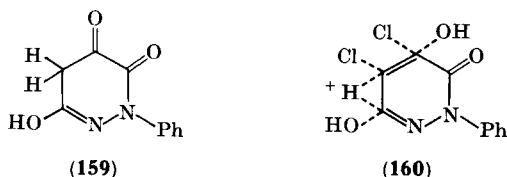
1-Aryl-3-pyrazolone-5-carboxylic acids (158) are obtained from 2-aryl-3(2*H*)-pyridazinones bearing halogen atoms at positions 4 and 6 (157, X = Cl),<sup>297, 704</sup> or a hydroxy or methoxy group and halogen (157, R = OH or OMe).<sup>437</sup> The same pyrazolonecarboxylic acid is also obtained from 1,2-disubstituted 5-halo-3,6-dioxo-1,2,3,6-tetrahydropyridazines.<sup>437</sup> The rearrangement is usually induced by 10% sodium hydroxide at about 120° for some hours; a lower concentration



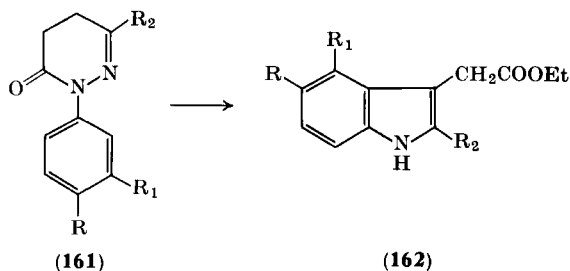
of alkali and milder reaction conditions cause only replacement of the halogen and from 157 (R = Ph, X = Cl) the 6-hydroxy derivative (157, R = Ph, X = OH) is obtained.<sup>466</sup> Similar treatment of 2-phenyl-4,6-diethoxy-3(2*H*)-pyridazinone with sodium hydroxide at 120–130° for 6 hours resulted only in the formation of the 4-hydroxy derivative, whereas rearrangement to 158 is achieved with hot concentrated hydrobromic acid.<sup>437</sup>

<sup>704</sup> Y. Maki, H. Kizu, and K. Obata, *Yakugaku Zasshi* **83**, 725 (1963).

As the 4,5-dimethoxy and 4,5,6-trimethoxy analogs with hydrobromic acid are transformed only into the corresponding hydroxypyridazinones, it has been postulated that **159** might be an essential intermediate for ring contraction. However, **158** has been obtained also from 2-phenyl-4,5-dichloro-3(2*H*)-pyridazinone and, to explain these rearrangements, two reaction mechanisms have been put forward. The foregoing rearrangement of the 4,5-dihalo analogs has been explained as to proceed through **160**.<sup>466</sup>



Rearrangement of a pyridazine into a pyrrole has been found when 3-anilinopyridazine is heated in the presence of Raney nickel; 2-anilino-2-pyrroline is formed in this reductive ring contraction.<sup>438</sup> Similarly, 2,3,4-triphenylpyrrole is obtained from 4,5,6-triphenyl-3(2*H*)-pyridazinethione<sup>705</sup> by reductive desulfurization with Raney nickel. A mechanism suggested for similar ring contractions of cinnolines into indoles<sup>706</sup> may be operating also in this case. Another



example is the formation of 1-tosylaminopyrrole from 1-tosyl-1,4-dihydropyridazine<sup>16</sup> and hot acids or from 1-tosyl-6-ethoxy-1,4,5,6-tetrahydropyridazine and cold hydrochloric acid.

<sup>705</sup> A. Pollak and M. Tišler, *Tetrahedron Letters*, 253 (1964).

<sup>706</sup> L. S. Besford and J. M. Bruce, *J. Chem. Soc.*, 4037 (1964).

Ring contraction of a pyridazine with concurrent cyclization to indole derivatives proceeds with 1-aryl-6-oxo-1,4,5,6-tetrahydropyridazines having at position 3 a carboxyl or methyl group (**161**).<sup>136, 137, 186, 707</sup> This reaction is usually performed in ethanolic solution containing hydrogen chloride or sulfuric acid, and also potassium hydroxide. Indoles of the general formula **162** ( $R_2 = \text{COOEt}$ ,  $\text{COOH}$ , or  $\text{Me}$ ) are obtained.

6-Methyl-1,4,5,6-tetrahydropyridazine when heated with  $\text{MeI}$  and then with aqueous sodium hydroxide is transformed into  $\gamma$ -dimethyl-aminovaleronitrile. This reaction is claimed to be the first example of an aminonitrile rearrangement of pyridazines.<sup>708</sup>

## V. Note Added in Proof

Since this review was written, pyridazine chemistry has been growing at an increasing rate, as might be expected. When reading the proof we felt inclined to summarize briefly the latest developments which have come to our attention.

A novel type of pyridazine ring formation has been found to proceed between diazomethane and tetrachlorocyclopropene giving 3,4,5-trichloropyridazine in good yield.<sup>709</sup> Another novel type of pyridazine ring formation is in the reaction of aci-nitropropenes with diazonium salts. The obtained intermediates were cyclized on heating to 2-aryl-4-carbalkoxy-6-nitro-3(2*H*)-pyridazinones.<sup>710</sup> Hydrogenation of the hydrazides of 3,5-dimethylisoxazole-4-carboxylic acid and the corresponding 5-methyl analog gave a mixture of a pyrazoline and 4-amino-6-methyl-3(2*H*)-pyridazinone.<sup>711</sup> Similarly, semicarbazones of 3-acylisoxazole derivatives on hydrogenolysis transform into 4-aminopyridazines.<sup>712</sup> Hydrogenation of isoxazolo[3,4-*d*]pyridazine-7-ones, isoxazolo[3,4-*d*]pyridazine-4,7-diones and isoxazolo[3,4-*d*]pyridazine-4-ones produced 5-acyl-4-amino-3(2*H*)-pyridazinones, 5-acyl-4-amino-6-hydroxy-3(2*H*)-pyridazinones, and

<sup>707</sup> M. Amorosa and L. Lipparini, *Ann. Chim. (Rome)* **47**, 722 (1957).

<sup>708</sup> K. N. Zelenin and V. G. Kameridinerov, *Zh. Organ. Khim.* **1**, 1899 (1965).

<sup>709</sup> H. M. Cohen, *J. Heterocyclic Chem.* **4**, 130 (1967).

<sup>710</sup> T. Severin, B. Brueck, and P. Adhikary, *Chem. Ber.* **99**, 3097 (1966).

<sup>711</sup> V. Sprio and E. Ajello, *Ann. Chim. (Rome)* **56**, 1103 (1966).

<sup>712</sup> V. Sprio and E. Ajello, *Ann. Chim. (Rome)* **57**, 846 (1967).

4-acyl-5-amino-3(2*H*)-pyridazinones, respectively.<sup>713</sup> Pyridazine derivatives are also formed in the reaction between monooximes of certain 1,5-diketones and hydrazine<sup>714</sup> and through the addition of styrene to substituted *s*-tetrazine.<sup>715</sup> Syntheses of some 3-hetaryl-substituted pyridazines,<sup>716</sup> 3(2*H*)-pyridazinones,<sup>717, 718, 719, 720, 721, 722</sup> and various sulfonamides incorporating the pyridazine nucleus<sup>723, 724, 725, 726</sup> are described.

3,4,5-Trimercaptopyridazine has been obtained by the action of P<sub>4</sub>S<sub>10</sub> on dipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin-1,6-dione.<sup>727</sup>

The structure of the self-condensation product of 3-chloro-6-methylpyridazine has been now proved on the basis of chemical and spectroscopic evidence to be correct, as suggested previously as 67.<sup>728</sup>

Synthesis of 1,2-disubstituted perhydro-3,6-pyridazinediones<sup>729</sup> and 6-( $\delta$ -carboxybutyl)-4,5-dihydro-3(2*H*)-pyridazinone<sup>730</sup> is reported. Tetrahydropyridazines were also synthesized from 3(2*H*)-pyridazinones by reduction with LiAlH<sub>4</sub>.<sup>718</sup>

<sup>713</sup> V. Sprio, E. Ajello, and A. Mazza, *Ann. Chim. (Rome)* **57**, 836 (1967).

<sup>714</sup> N. A. Evans, R. B. Johns, and K. R. Markham, *Austral. J. Chem.* **20**, 713 (1967).

<sup>715</sup> H. H. Takimoto and G. C. Denault, *Tetrahedron Letters*, 5369 (1966).

<sup>716</sup> G. P. Sokolov and S. A. Giller, *Khim. Geterotsikl. Soedin.*, 556 (1967).

<sup>717</sup> C. G. Wermuth, *Chimie Thérapeutique* **2**, 130 (1967).

<sup>718</sup> G. Leclerc, C. G. Wermuth, *Bull. Soc. Chim. France*, 1307 (1967).

<sup>719</sup> T. Takahashi, Y. Maki, H. Kizu, M. Takaya, and T. Miki, *Yakugaku Zasshi* **86**, 1082 (1966).

<sup>720</sup> T. Takahashi, Y. Maki, H. Kizu, M. Takaya, and T. Miki, *Yakugaku Zasshi* **86**, 1168 (1966).

<sup>721</sup> S. H. Schroeter, R. Appel, R. Brammer, and G. O. Schenk, *Ann. Chem.* **697**, 42 (1966).

<sup>722</sup> V. Zikan and M. Semonsky, *Coll. Czech. Chem. Commun.* **32**, 2374 (1967).

<sup>723</sup> T. Nakagome, A. Kobayashi, A. Misaki, T. Komatsu, T. Mori, and S. Nakanishi, *Chem. Pharm. Bull. Japan* **14**, 1065 (1966).

<sup>724</sup> T. Nakagome, A. Kobayashi, and A. Misaki, *Chem. Pharm. Bull. Japan* **14**, 1074 (1966).

<sup>725</sup> T. Nakagome, A. Misaki, and T. Komatsu, *Chem. Pharm. Bull. Japan* **14**, 1082 (1966).

<sup>726</sup> V. Bedenko and B. Glunčić, *Croat. Chem. Acta* **38**, 309 (1966).

<sup>727</sup> R. N. Castle, K. Kaji, and D. Wise, *J. Heterocyclic Chem.* **3**, 541 (1966).

<sup>728</sup> H. Lund and S. Gruhn, *Acta Chem. Scand.* **20**, 2637 (1966).

<sup>729</sup> E. P. Rosenquist, *Diss. Abstr.* **B27**, 185 (1966).

<sup>730</sup> R. G. Kitner and N. V. Savitskaya, *Khim. Geterotsikl. Soedin.* **946** (1966).

Condensation products of pyridoxal phosphate and hydrazinopyridazines<sup>731</sup> and of sulfamethoxypyridazine or sulfachloropyridazine and xanthidrol were prepared.<sup>732</sup>

Polarographic reduction of 3,6-diphenylpyridazine and 1-methyl-3,6-diphenylpyridazinium iodide was studied.<sup>733</sup>

Under the influence of  $\text{HgBr}_2$  6-(tetraacetyl- $\beta$ -D-glucosyloxy)-3(2H)-pyridazinone is transformed into a mixture of 2-(tetraacetyl- $\beta$ -D-glucosyl)-6-(tetraacetyl- $\beta$ -D-glucosyloxy)-3(2H)-pyridazinone and 2-tetraacetyl- $\beta$ -D-glucosyl)-6-(tetraacetyl- $\alpha$ -D-glucosyloxy)-3(2H)-pyridazinone.<sup>734</sup> A similar reaction was observed with the related 3,6-bisglucoside.

The Mannich reaction of various 3(2H)-pyridazinones with 2,2'-dichlorodiethylamine was investigated.<sup>735</sup> In few cases the expected nitrogen-mustard derivatives were obtained, but in most cases N-hydroxymethyl derivatives were isolated. With other amines the corresponding N-Mannich bases were formed in good yields. Reaction with 4(1H)-pyridazinones was also investigated.

The reaction of 4,5-dichloro-2-(2-carboxyethyl)-3(2H)-pyridazinone with thiols was studied by kinetic measurements.<sup>736</sup> It was established to be an  $\text{S}_{\text{N}}2$ -reaction with  $\text{RS}^-$  as the nucleophilic agent.

Quaternization of pyridazine derivatives is described.<sup>737, 738</sup> Methyl iodide in acetonitrile gave in most cases a mixture of isomers. The composition of the quaternization mixture is determined mainly by steric and inductive effects.<sup>738</sup>

Reaction of 4-amino-6-methoxypyridazine or 4-amino-3(2H)-pyridazinone with tosyl chloride gave a mixture of products tosylated at the 4-amino group or at the oxygen of the ring amide group.<sup>725</sup> 4-Amino-3,6-dimethoxypyridazine afforded under similar reaction

<sup>731</sup> T. Duhault, P. Gonnard, and S. Fenard, *Bull. Soc. Chim. Biol.* **49**, 177 (1967).

<sup>732</sup> R. E. Moskalyk and L. G. Chatten, *Can. J. Chem.* **45**, 1411 (1967).

<sup>733</sup> H. Lund, *Oesterr. Chemiker-Z.* **68**, 43 (1967).

<sup>734</sup> G. Wagner and D. Heller, *Pharmazie* **21**, 592 (1966).

<sup>735</sup> S. Kamiya, A. Nakamura, T. Itai, K. Koshinuma, and G. Okusa, *Yakugaku Zasshi* **86**, 1099 (1966).

<sup>736</sup> W. Schreiber, *Hoppe-Seylers Z. Physiol. Chem.* **348**, 371 (1967).

<sup>737</sup> D. G. Farnum, R. J. Alaimo, and J. M. Dunston, *J. Org. Chem.* **32**, 1130 (1967).

<sup>738</sup> H. Lund and P. Lunde, *Acta Chem. Scand.* **21**, 1067 (1967).

conditions a mixture of several tosylated and demethylated products.<sup>725</sup> A methylsulfonyl group in pyridazine derivatives was substituted by methoxide ion.<sup>739</sup> Methylation of 4-amino-3(2*H*)-pyridazinones with dimethylsulfate in aqueous sodium hydroxide solution yielded the corresponding 2-methyl derivatives and the zwitterionic 1-methyl compound.<sup>740</sup> The ratio of the formation of both types has been found to be markedly influenced by the substituent at position 6.

Reaction of 3,6-dimethoxy-4-nitropyridazine 1-oxide with methyl or ethyl iodide gave 2,5,6-trimethoxy-3(2*H*)-pyridazinone or 2,5-diethoxy-6-methoxy-3(2*H*)-pyridazinone.<sup>741</sup> Transesterification reactions in different alkoxy pyridazine *N*-oxides with sodium methoxide or ethoxide were studied.<sup>742</sup> These reactions were found to proceed under mild conditions; dialkoxy compounds underwent hydrolysis to form the hydroxy compounds. In the dimethoxy compound the 3 position is more reactive than the 6 position, while this is reversed in the diethoxy compound. Methoxy group was found to be more sensitive to the exchange than the ethoxy group.<sup>742</sup>

Rearrangement of 2-phenyl-4,6-dichloro-3(2*H*)-pyridazinone into 1-phenyl-3-pyrazolone-5-carboxylic acid, described previously,<sup>704</sup> is recorded in connection with the synthesis of some pyrazolone derivatives.<sup>743</sup>

Probable formation of cyclobutadiene-type cations in the mass spectral decomposition of pyridazines was reported.<sup>744, 745</sup>

Additional studies concerning the conformation of hydrogenated pyridazine derivatives were performed.<sup>746, 747, 748</sup>

The electron spectra of neutral pyridazines and coordinated pyridazine adducts were calculated by the SCF method.<sup>749</sup>

<sup>739</sup> G. B. Barlin and W. V. Brown, *J. Chem. Soc., B, Phys. Org.* **648** (1967).

<sup>740</sup> T. Nakagome, A. Misaki, and A. Murano, *Chem. Pharm. Bull. (Tokyo)* **14**, 1090 (1966).

<sup>741</sup> M. Yanai and T. Kinoshita, *Yakugaku Zasshi* **86**, 1124 (1966).

<sup>742</sup> M. Yanai and T. Kinoshita, *Yakugaku Zasshi* **87**, 114 (1967).

<sup>743</sup> T. Takahashi, M. Farukawa, and Y. Maki, *Yakugaku Zasshi* **86**, 867 (1966).

<sup>744</sup> M. H. Benn, T. S. Sørensen, and A. M. Hogg, *Chem. Commun.*, 574 (1967).

<sup>745</sup> S. J. Weininger and E. R. Thornton, *J. Amer. Chem. Soc.* **89**, 2950 (1967).

<sup>746</sup> B. Junge and H. A. Staab, *Tetrahedron Letters*, 709 (1967).

<sup>747</sup> R. M. Moriarty, M. R. Murphy, S. J. Druck, and L. May, *Tetrahedron Letters*, 1603 (1967).

<sup>748</sup> B. H. Korsch and N. V. Riggs, *Tetrahedron Letters*, 5897 (1966).

<sup>749</sup> P. G. Perkins, *J. Mol. Spectrosc.* **22**, 464 (1967).

Solvent effects on the fluorescence spectrum<sup>750</sup> and the effect of protonation on electron density and chemical shift in NMR spectrum of pyridazine<sup>751</sup> were investigated.

<sup>750</sup> H. Baba, L. Goodman, and P. C. Valenti, *J. Amer. Chem. Soc.* **88**, 5410 (1966).

<sup>751</sup> W. Adam, A. Grimison, and G. Rodriguez, *Tetrahedron* **23**, 2513 (1967).

# Recent Advances in the Chemistry of Phenothiazines

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## I. Introduction

### A. SCOPE OF THE CHAPTER

The first synthesis of phenothiazine was reported by Bernthsen<sup>1</sup> about 80 years ago. In the evolution of the chemistry of this heterocycle, three periods can be discerned. First, phenothiazine was of interest owing to its quinonoid derivatives—an important chapter in sulfur dye chemistry. Research work in the field of phenothiazine was then stimulated by the discovery of the anthelmintic action of unsubstituted and of some *C*-substituted phenothiazines. During the last two decades, the exceptional pharmacological properties of some *N*-substituted phenothiazines, e.g., the antihistaminic activity of promethazine, 10-(2-dimethylamino-1-propyl)phenothiazine, and particularly the psychotherapeutic action of chlorpromazine, 2-chloro-10-(3-dimethylamino-1-propyl)phenothiazine, focused interest mainly on the synthesis and testing of a great number of compounds of this type. The phenothiazine drugs now play a very important part in chemotherapy.

It is more and more obvious that a deeper knowledge of the physical and chemical properties of the phenothiazine ring is necessary for the synthesis of new biologically active phenothiazine derivatives, and for the understanding of the mechanism of their interaction with living organisms. Consequently, along with the great amount of work concerning the preparation and testing of very similar phenothiazine derivatives—the difference between them consisting usually only of small modifications at the end of a side chain—fundamental research in this field has been carried out more intensively during the last 5 or 6 years.

The last comprehensive survey on chemical reactivity of phenothiazine is that of Massie (1954).<sup>2</sup> Since then, many significant results have been reported which are of interest not only for workers in the

<sup>1</sup> A. Bernthsen, *Ber. Deut. Chem. Ges.* **16**, 2896 (1883).

<sup>2</sup> S. P. Massie, *Chem. Rev.* **54**, 797 (1954).

phenothiazine field, but also for the entire heterocyclic chemistry. Short reviews on phenothiazines are given in *Chemistry of Carbon Compounds*,<sup>3</sup> and in Elderfield's *Heterocyclic Chemistry*.<sup>3a</sup> The present authors aim in giving a detailed discussion of the material published after Massie's review, including papers indexed by *Chemical Abstracts* up to November 1966. Papers concerning the synthesis of *N*-substituted phenothiazines of potential practical interest are dealt with only when the chemistry of the phenothiazine ring is directly involved in the chemical processes reported. For phenothiazine derivatives with aminoalkyl side chains, the reader is referred to the review of Schenker and Herbst<sup>4</sup>; tables containing 3957 substances accompany this work. There are also some other compilations on phenothiazine drugs, concerning mainly their preparation,<sup>5</sup> use in therapy,<sup>6-10</sup> the correlation between structure and pharmacological activity,<sup>11-15</sup> and metabolic fate.<sup>16, 17</sup> An annotated bibliography of phenothiazine and of its derivatives between 1934 and 1958, particularly useful for documentation on anthelmintic action, was published by Folse.<sup>18</sup>

<sup>3</sup> G. R. Ramage, E. H. Rodd, and J. K. Landquist, in "Chemistry of Carbon Compounds IVC, Heterocyclic Compounds" (E. H. Rodd, ed.), Chapter XVI. Elsevier, Amsterdam, 1960.

<sup>3a</sup> D. E. Pearson, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, Chapter XIV, p. 624. Wiley, New York, 1957.

<sup>4</sup> E. Schenker and H. Herbst, *Progr. Drug Res.* **5**, 269 (1963).

<sup>5</sup> J. Sykalski, *Wiadomosci Chem.* **20**, 1 (1966); *Chem. Abstr.* **64**, 11206d (1966).

<sup>6</sup> H. Kleinsorge and K. Rösner, "Die Phenthiazinderivate in der Medizin, Klinik und Experiment," Fischer, Jena, 1958.

<sup>7</sup> J. Blazek, V. Spinkova, and Z. Stijskal, *Pharmazie* **17**, 497 (1962).

<sup>8</sup> J. Blazek, *Pharm. Praxis, Beil.* "Pharmazie," 85 (1963).

<sup>9</sup> R. Toelle, *Med. Klin. (Munich)* **59**, 801 (1964).

<sup>10</sup> A. Moggi, *Igiene Sanita Pubblica (Rome)* **22**, 52 (1966); *Chem. Abstr.* **65**, 7803f (1966).

<sup>11</sup> F. Mietzsch, *Angew. Chem.* **66**, 363 (1954).

<sup>12</sup> Yu. I. Vikhlyaev, *Uch. Zap. Inst. Farmakol. i Khimioterapii, Akad. Med. Nauk SSSR* **1**, 27 (1958); *Chem. Abstr.* **54**, 23039h (1960).

<sup>13</sup> A. Lespagnol, *Bull. Soc. Chim. France*, 1291 (1960).

<sup>14</sup> M. Gordon, L. Cook, D. H. Tedeschi, and R. E. Tedeschi, *Arzneimittel-Forsch.* **13**, 318 (1963).

<sup>15</sup> M. Gordon, P. N. Craig, and C. L. Zirkle, *Advan. Chem. Ser.* **45**, 140 (1964).

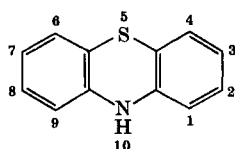
<sup>16</sup> J. L. Emmerson and T. S. Miya, *J. Pharm. Sci.* **52**, 411 (1963).

<sup>17</sup> C. J. Carr, *Ann. N.Y. Acad. Sci.* **96**, 170 (1962).

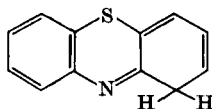
<sup>18</sup> D. S. Folse, *Kansas, Agr. Expt. Sta., Tech. Bull.* **115**, 1 (1961).

## B. NOMENCLATURE

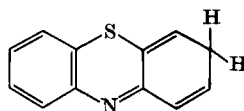
The name "phenothiazine" and the numbering given in the *Revised Ring Index*,<sup>19</sup> used in *Chemical Abstracts*, and recommended by the *IUPAC Rules of Organic Nomenclature*<sup>20</sup> will be used throughout this chapter. The *o*- and *p*-quinonoid forms of phenothiazine,



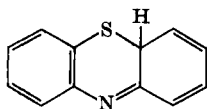
Phenothiazine  
(10H-Phenothiazine)



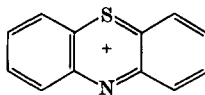
1H-Phenothiazine



3H-Phenothiazine



4aH-Phenothiazine



Phenazathionium  
cation

namely 1H-, 3H-, and 4aH-phenothiazine, are represented until now only by 3H-phenothiazines in which both hydrogen atoms in position 3 are substituted. When oxygen is the substituent, 3H-phenothiazine-3-one is obtained; the short name "phenothiazone" was preferred for this substance.

The cation obtained on two-electron oxidation of phenothiazine will be referred to as the "phenazathionium cation."

## II. New Methods of Preparation of Phenothiazines via Ring Closure

Some new variants of the thionation of diphenylamines and of the cyclization of suitably substituted diphenyl sulfides—the two well-known principal routes to the phenothiazine ring—have recently been developed.

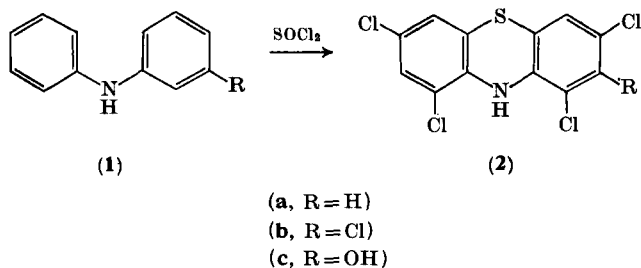
<sup>19</sup> A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd ed., RRI 3314. Am. Chem. Soc., Washington, D.C., 1960.

<sup>20</sup> IUPAC Rules of Organic Nomenclature, *Bull. Soc. Chim. France*, 1258 (1958).

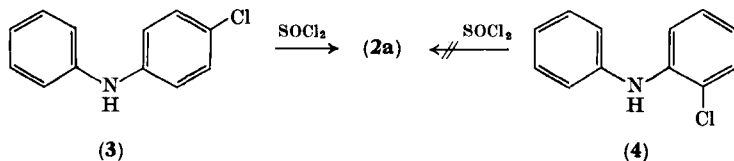
## A. THIONATION OF DIPHENYLAMINES

A patent claims the preparation of *N*-substituted phenothiazines from the corresponding diphenylamines using  $\text{SOCl}_2$  in benzene as a thionating agent.<sup>21</sup> There is no mention of chlorination as a side reaction, although with  $\text{S}_2\text{Cl}_2$ , which is less reactive in this respect, chlorination seems to accompany the thionation (see Section V, A, 1, *d*).

Kanô and Fujimoto<sup>22</sup> obtained polychlorophenothiazines using thionyl chloride as a thionating agent. Unsubstituted diphenylamine (**1a**) yielded 1,3,7,9-tetrachlorophenothiazine (**2a**).



3-Substituted diphenylamines react in the same way,<sup>23</sup> and the formation of small amounts of 4-substituted phenothiazines is observed,<sup>22</sup> a feature also encountered in other thionation reactions.<sup>2</sup> Phenothiazine could be obtained neither from nitrodiphenylamines nor, surprisingly, from *N*-phenyltoluidines. Also surprising is the



failure of thionation in the case of 2-chlorodiphenylamine (**4**), especially when compared with the normal behavior of 4-chlorodiphenylamine (**3**).<sup>23</sup>

Other *C*-substituted diphenylamines carrying electron-donor substituents ( $-\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{NH}_2$ , etc.) were cyclized to chlorinated

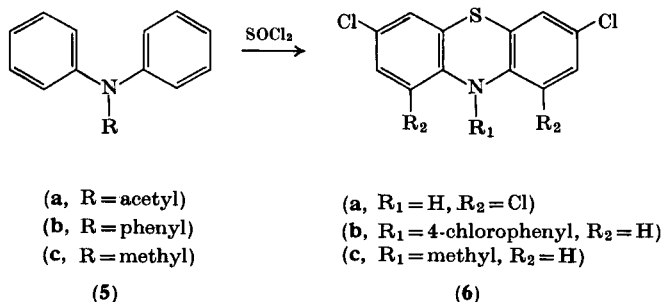
<sup>21</sup> Sandoz Ltd., British Patent 890,912; *Chem. Abstr.* **58**, 1472g (1963).

<sup>22</sup> H. Kanô and M. Fujimoto, *Pharm. Bull. (Tokyo)* **5**, 393 (1957).

<sup>23</sup> M. Fujimoto, *Bull. Chem. Soc. Japan* **32**, 294 (1959).

phenothiazines by  $\text{SOCl}_2$ , the chlorine atoms probably entering ortho to the preexisting substituents.<sup>24</sup>

*N*-Substituted diphenylamines also yielded phenothiazines on treatment with  $\text{SOCl}_2$ .<sup>24</sup> Thus, *N*-acetyldiphenylamine (**5a**) was quantitatively converted into tetrachlorophenothiazine (**2a**) while *N*-phenyldiphenylamine (triphenylamine) (**5b**) gave 3,7-dichloro-10-(4'-chlorophenyl)phenothiazine (**6b**) in 91% yield. In the first case



the chlorine atoms that entered positions 1 and 9 promote the removal of the acyl group from position 10; in the second case, the bulky substituent attached to nitrogen prevents the replacement of the hydrogens from positions 1 and 9 by chlorine (see Sections IV, G, 4 and V, A, 1, b). The behavior of *N*-methyldiphenylamine (**5c**) is intermediate in this respect; 3,7-dichloro-10-methylphenothiazine (**6c**) was isolated in this case in 7% yield, along with **2a**.

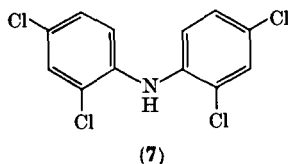
The conversion of diphenylamines into chlorophenothiazines by  $\text{SOCl}_2$  obviously involves two principal processes, namely the cyclization and the chlorination; the question arises as to which is the first step.<sup>23</sup> Phenothiazine, 2-chloro-, and 4-chlorophenothiazine are chlorinated by thionyl chloride yielding products identical to those obtained from the corresponding diphenylamines, whereas 2,4,2',4'-tetrachlorodiphenylamine (**7**), cannot be cyclized on treating with  $\text{SOCl}_2$ . Consequently, ring closure takes place prior to chlorination.

The reaction of diphenylamines with  $\text{SOBr}_2$  and  $\text{SO}_2\text{Cl}_2$  leads only to halogenated diphenylamines.<sup>22</sup>

Reaction kinetics and thermodynamic and technological parameters, characterizing the thionation of diphenylamine with sulfur in

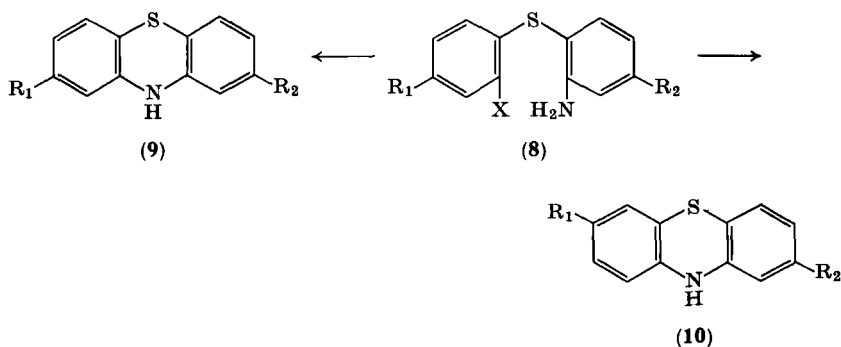
<sup>24</sup> M. Fujimoto, *Bull. Chem. Soc. Japan* **32**, 296 (1959).

the presence of  $\text{AlCl}_3$  or iodine, have been determined under conditions similar to those encountered in the large-scale manufacture of phenothiazine.<sup>25</sup>



### B. CYCLIZATION OF DIPHENYL SULFIDES

The synthesis of phenothiazines starting with *o*-amino-*o'*-halogenodiphenyl sulfides has been a controversial problem, inasmuch as compounds like **8** may undergo an Ulmann-type cyclization to 2,8-disubstituted phenothiazines (**9**), or, through a Smiles rearrangement, may give 2,7-disubstituted phenothiazines (**10**).



It was earlier stated<sup>26</sup> that the reaction proceeds only following the pathway of the Ulmann cyclization. Evidence has been recently put forward<sup>27, 28</sup> that in some cases there is a Smiles rearrangement and

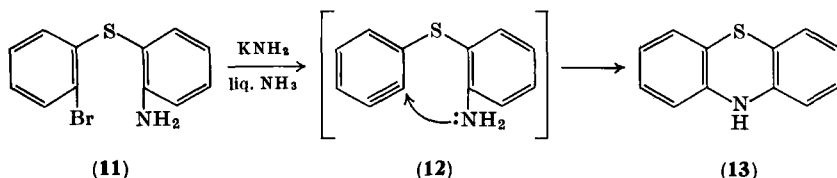
<sup>25</sup> D. Elenkov, P. Petrov, and V. Tsochev, *Godishnik Khim.-Tekhnol. Inst.* **11**, 35 (1964); *Chem. Abstr.* **65**, 13696c (1966).

<sup>26</sup> J. G. Michels and E. D. Amstutz, *J. Am. Chem. Soc.* **72**, 888 (1950).

<sup>27</sup> G. Pappalardo and G. Scapini, *Bol. Sci. Fac. Chim. Ind. Bologna* **21**, 143 (1963); *Chem. Abstr.* **59**, 13972e (1963).

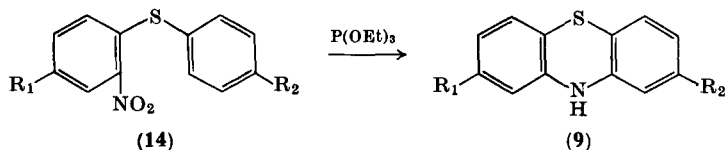
<sup>28</sup> E. A. Nodiff and M. Hausman, *J. Org. Chem.* **29**, 2453 (1964).

the products **10** are obtained. In the halogen-carrying ring of **8** there are two reaction centers which may undergo nucleophilic attack by the amine nitrogen: the carbon atom to which the sulfur bridge is attached, and the carbon atom carrying the halogen. Usually, the latter is more reactive and products like **9** are formed. In those cases when the nature and position of the substituents in the halogen-carrying ring result in a greater positive charge on the carbon atom attached to sulfur (e.g.,  $R_1 = -NO_2$ ), the Smiles rearrangement occurs yielding products like **10**.



Hrutford and Bunnett<sup>29</sup> obtained phenothiazine in 35% yield on treatment of *o*-amino-*o'*-bromodiphenyl sulfide (**11**) with  $KNH_2$  in liquid ammonia and assumed that a benzyne system **12** was an intermediate in the reaction.

This method can be applied to other heterocyclic systems. It would be interesting to prove whether or not the same reaction pathway is followed when there are other substituents on the halogen-carrying ring, since it is known that with sodium amide in benzene the *o*-amino-*o'*-bromodiphenyl ethers undergo Smiles rearrangements.<sup>30</sup>



Cadogan *et al.*<sup>31</sup> performed a reductive cyclization of *o*-nitro-diphenyl sulfide (**14**) to phenothiazines (**9**) using triethyl phosphite. In the case of unsubstituted phenothiazine, the yield was 54%.

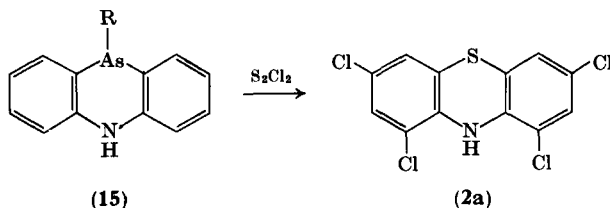
<sup>29</sup> B. F. Hrutford and J. F. Bunnett, *J. Am. Chem. Soc.* **80**, 2021 (1958).

<sup>30</sup> G. E. Bonvicino, L. H. Yogodzinski, and R. A. Hardy, Jr., *J. Org. Chem.* **27**, 4272 (1962).

<sup>31</sup> J. I. G. Cadogan, R. K. Mackie, and M. J. Todd, *Chem. Commun.*, 491 (1966).

## C. OTHER METHODS

Spasov and Zhechev<sup>32</sup> prepared tetrachlorophenothiazine (2a) by the action of  $S_2Cl_2$  on 10-chloro-5,10-dihydrophenarsazine (15,  $R=Cl$ ) and other 10-substituted 5,10-dihydrophenarsazines (15). In



a violent reaction there is replacement of arsenic by sulfur and chlorination. Inasmuch as phenothiazine and diphenylamine are not converted into tetrachlorophenothiazine by  $S_2Cl_2$ <sup>32</sup> (cf., however, Section V, A, 1, d) the hypothesis that phenarsazine is chlorinated prior to the removal of arsenic appears as a very natural one. The failure of the reaction in the case of *N*-acyl and *C*-nitroderivatives of 10-chloro-5,10-dihydrophenarsazine supports this interpretation.

## III. Molecular Structure and Physical Properties

## A. MOLECULAR ORBITAL TREATMENTS

1. *Energy Levels and Electron-Donating Properties of Phenothiazines*

In 1959 two research groups independently reported that molecular orbital treatment of phenothiazines using the Hückel approximation indicates that the highest filled molecular orbital is not only a very highly situated, but, even in nonexcited states, an antibonding orbital.

Thus, Pullman and Pullman,<sup>33</sup> after showing that in the reduced forms of riboflavin-type coenzymes the highest filled level corresponds to an antibonding orbital, found that leukomethylene blue, another excellent electron donor, displays the same quantum mechanical feature, although methylene blue, the oxidized form, is a good electron acceptor. This provides a theoretical explanation for the observation

<sup>32</sup> Al. Spasov and M. Zhechev, *Bull. Inst. Chim. Acad. Bulgare Sci.* **2**, 67 (1953); *Chem. Abstr.* **49**, 5492e (1955).

<sup>33</sup> B. Pullman and A. Pullman, *Biochim. Biophys. Acta* **35**, 535 (1959).



that methylene blue can alternatively act as hydrogen donor and acceptor in respiration, as shown by Szent-Györgyi.<sup>34</sup>

On the other hand, Karreman *et al.*,<sup>35</sup> considering that the action of drugs on the central nervous system may be due to a charge transfer at the electric double layer of the cell surface, investigated whether or not there is a correlation between the remarkable neuroleptic action of 2-chloro-10-(3-dimethylamino-1-propyl)phenothiazine (chlorpromazine) and its molecular electronic properties. LCAO calculations showed that the  $K$  value in the expression for the energy of the highest filled orbital is negative; that is, this orbital is an antibonding one. This is particularly striking in the case of chlorpromazine inasmuch as this is a molecule in its normal, stable state, and not a substance on which H atoms were forced, as in leukomethylene blue. Phenothiazine itself is also characterized by a negative  $K$  value of the highest filled orbital; consequently, the strong electron-donating properties of chlorpromazine are linked with the heterocyclic part of the molecule.

Orloff and Fitts,<sup>36</sup> taking into account the participation of the  $d$  orbitals of sulfur, obtained results that differ significantly from the above; the highest filled molecular orbital now appears bonding, although the calculations still indicate that phenothiazine, chlorpromazine, and leukomethylene blue are strong electron donors. In this case, another explanation for the instability of leukomethylene blue is required. The contradictory results reported until now are due primarily to the approximate character of the Hückel method and to the somewhat arbitrary choice of starting parameters. There appears to be no sound reason to prefer either one or another of the recorded results.

Whatever the case may be, the excellent electron-donating properties of phenothiazine are well-established. The ionization potentials are low, as indicated indirectly by charge-transfer spectra<sup>37, 38</sup> and directly by photoelectric work in the solid state,<sup>39, 40</sup> from which the value 4.36 eV was derived for the ionization potential.<sup>40</sup>

<sup>34</sup> A. Szent-Györgyi, *Biochem. Z.* **150**, 195 (1924).

<sup>35</sup> G. Karreman, I. Isenberg, and A. Szent-Györgyi, *Science* **130**, 1191 (1959).

<sup>36</sup> M. K. Orloff and D. D. Fitts, *Biochim. Biophys. Acta* **47**, 596 (1961).

<sup>37</sup> M. Kinoshita, *Bull. Chem. Soc. Japan* **35**, 1609 (1962).

<sup>38</sup> R. Beukers and A. Szent-Györgyi, *Rec. Trav. Chim.* **81**, 255 (1962).

<sup>39</sup> L. E. Lyons and J. C. Mackie, *Nature* **197**, 589 (1963).

<sup>40</sup> D. A. Kearns and M. Calvin, *J. Chem. Phys.* **34**, 2026 (1961).

It may be also mentioned that phenothiazine is one of the rare organic compounds in which mass spectrometry has revealed triply charged ions.<sup>41</sup>

## 2. Molecular Configuration of Phenothiazines

The configuration of the molecule is important, affecting the significance of the results of the Hückel molecular orbital treatment. No agreement has been reached until now whether the phenothiazine molecule is, at least nearly, planar, or whether it is folded along the axis passing through the two heteroatoms. It was stated by Wood *et al.*<sup>42</sup> on the basis of crystallographic studies that the molecule could be planar. Subsequently, Leonard and Sutton<sup>43</sup> interpreted dipole moment measurements as evidence for the existence of a dihedral angle of  $145 \pm 5^\circ$  between the planes of the benzene rings of phenothiazine. This problem is of major importance for the interpretation of ESR spectra of *N*-substituted phenothiazinyl radicals (see Section IV, D).

In a theoretical approach to this question, Malrieu and Pullman<sup>44</sup> pointed out that two extreme types of configuration are to be taken into account in the case of phenothiazine, namely the planar configuration and the "tetragonal folded" one. In the latter, the nitrogen and sulfur are in the  $sp^3$  hybridization state and the planes containing the benzene rings are folded along the axis passing through *N* and *S*. The hydrogen atom attached to nitrogen can now adopt two distinct configurations, called "H-intra"—with the hydrogen pointing inside—and "H-extra"—when the hydrogen points outside with respect to the dihedral angle (Fig. 1).

The two forms "H-intra" and "H-extra" are not electronically equivalent. In the "H-intra" configuration the lone pair of the nitrogen has an orientation which favors the conjugation with the benzene  $\pi$  systems, whereas in the "H-extra" configuration the lone pair is pushed toward the median plane of the molecular  $\pi$  orbital of the benzene rings. 10-Unsubstituted phenothiazines adopt the more advantageous configuration "H-intra," as shown by Malrieu and Pullman, who obtained satisfactory agreement between the

<sup>41</sup> S. Meyerson and R. W. Vander Haar, *J. Chem. Phys.* **37**, 2458 (1962).

<sup>42</sup> R. G. Wood, C. H. McCole, and G. Williams, *Phil. Mag.* [7] **31**, 79 (1941).

<sup>43</sup> N. J. Leonard and L. E. Sutton, *J. Am. Chem. Soc.* **70**, 1564 (1948).

<sup>44</sup> J. P. Malrieu and B. Pullman, *Theoret. Chim. Acta* **2**, 293 (1964).

calculated and experimental spin densities of the corresponding free radical<sup>44, 45</sup> (see Section IV, B, 3). The presence of a substituent at position 10 renders the configuration "intra" improbable for steric reasons, thus diminishing the participation of the nitrogen in the delocalized electronic system and lowering the energy of the highest

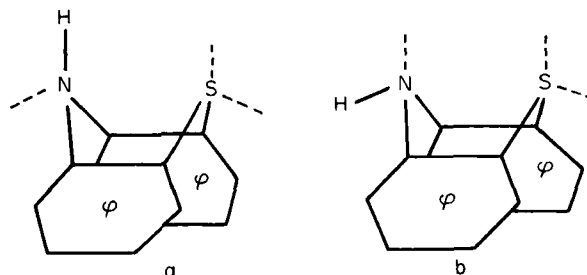


FIG. 1. "Tetragonal folded" configurations: (a) "H-extra"; (b) "H-intra."

filled molecular orbital. This provides an explanation for the apparently paradoxical fact that the introduction of an alkyl group in position 10 results in a diminution of the reactivity toward electrophilic reagents, and in an increase in the oxidation potential—whereas the introduction of the same substituent in other positions of the phenothiazine ring affects the chemical and physical behavior of the molecule in the usual, i.e., contrary, fashion.

It would be interesting to investigate whether or not such configurational effects are also encountered in other structurally related molecules, like phenoxazine, phenoselenazine, etc. The paper of Malrieu and Pullman<sup>46</sup> on isoalloxazines is a start in this direction.

Work is needed to verify whether or not some particular phenomena observed with 10-substituted phenothiazines, like the "polymorphism" of 10-methylphenothiazine-5-oxide<sup>47</sup> and the thermal behavior of chlorpromazine,<sup>48, 49</sup> are correlated with configurational differences.

<sup>45</sup> A. Pullman, *J. Chim. Phys.* **61**, 1666 (1964).

<sup>46</sup> J. P. Malrieu and B. Pullman, *Theoret. Chim. Acta* **2**, 302 (1964).

<sup>47</sup> G. P. Brown, J. W. Cole, and T. I. Crowell, *J. Org. Chem.* **20**, 1772 (1955).

<sup>48</sup> F. Gutmann and A. Netschey, *Nature* **191**, 1390 (1961).

<sup>49</sup> F. Gutmann and A. Netschey, *J. Chem. Phys.* **36**, 2355 (1962).

## B. ELECTRICAL PROPERTIES

As phenothiazine and its derivatives are excellent electron donors (see Section III,A,1), interesting electrical properties are to be expected with these compounds. Phenothiazine itself is a semiconductor as shown by Brown and Aftergut<sup>50</sup>; the activation energy is 1.6 eV between 50° and 150° for samples purified by sublimation and zone melting. The electrical parameters are influenced to an important extent by the method of sample preparation.

Interesting ideas are put forward by Gutmann and Netschey<sup>48, 49</sup> in papers on the electrical properties of chlorpromazine. This substance, as the free base, in a glassy amorphous state, is a semiconductor. The plot of  $\log R$  vs  $1/T$  shows that at about 32° the temperature coefficient of the resistivity changes sign, a phenomenon interpreted by the authors as a consequence of a "crystalline transition." In order to check the existence of the transition at 32°, thermal analysis, dielectric constant, and infrared spectral measurements were also performed. The authors emphasize that the differences between IR spectra before and after the transition are consistent with a change in the molecular configuration, involving both the side chain and the heterocyclic ring. They assumed that at low temperatures the side chain is folded over the molecule, but above 32° the molecule becomes roughly planar. As a consequence of these changes in conformation, modifications of the spatial distribution of the molecules may occur, accounting for the described electrical phenomena (see also Section III,A,2).

Subsequently, Kronick and Labes,<sup>51</sup> working on single crystals of chlorpromazine, grown from ethereal solutions, obtained specific resistivities of  $10^{15} \Omega\text{-cm}$ , that is,  $10^4$  times greater than those found by Gutmann and Netschey<sup>48, 49</sup> for glassy chlorpromazine, and the existence of a significant change in electrical properties associated with crystalline transition is considered doubtful—a conclusion supported by other literature data (see, for example, LeBlanc<sup>52</sup> and Murrell<sup>53</sup>). Although the values of the resistivity for glassy chlorpromazine samples were confirmed,<sup>54</sup> the problem needs further elucidation.

<sup>50</sup> G. P. Brown and S. Aftergut, *Nature* **193**, 361 (1962).

<sup>51</sup> P. L. Kronick and M. M. Labes, *J. Chem. Phys.* **38**, 776 (1963).

<sup>52</sup> O. H. LeBlanc, Jr., *J. Chem. Phys.* **35**, 1275 (1961).

<sup>53</sup> J. N. Murrell, *Mol. Phys.* **4**, 205 (1961).

<sup>54</sup> F. Gutmann and H. Keyser, *Nature* **205**, 1102 (1965).

## C. SPECTROSCOPY OF PHENOTHIAZINES

1. *Electronic Spectra*

The ultraviolet (UV) and visible spectra of some phenothiazines were recorded for analytical purposes (characterization, identification, and dosage).<sup>55-61</sup> Spectrophotometric studies on the colored

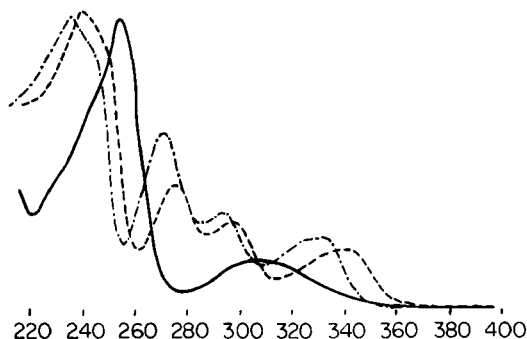


FIG. 2. Ultraviolet spectra. Key:—, phenothiazine; -----, 5-oxide; —.—, 5,5-dioxide.

oxidation products obtained by the action of various oxidants are dealt with in Section IV.

The oxidation at sulfur to the 5-oxide and 5,5-dioxide greatly modifies the UV spectrum, a characteristic pattern with four maxima being observed, as shown in Fig. 2.<sup>62</sup> This fact has found analytical applications.<sup>63</sup> A striking example of the analytical value of the UV

<sup>55</sup> J. Cymerman-Craig and W. K. Warburton, *Australian J. Chem.* **9**, 294 (1956).

<sup>56</sup> L. W. Bradford and J. W. Brackett, *Mikrochim. Acta*, 353 (1958).

<sup>57</sup> E. Angadji and J.-C. Colleter, *Bull. Soc. Pharm. Bordeaux* **101**, 147 (1962).

<sup>58</sup> A. H. Beckett and S. H. Curry, *J. Pharm. Pharmacol.* **15**, Suppl. 246 (1963).

<sup>59</sup> J.-C. Colleter, M. Gadret, and C. Bregere, *Bull. Soc. Pharm. Bordeaux* **103**, 224 (1964).

<sup>60</sup> C. Bodea, V. Fărcășan, and I. Oprean, *Rev. Roumaine Chim.* **10**, 1103 (1965).

<sup>61</sup> N. A. Kudryavtseva, Z. V. Pushkareva, and M. V. Startseva, *Zh. Organ. Khim.* **1**, 364 (1965); *Chem. Abstr.* **62**, 14664f (1965).

<sup>62</sup> R. J. Warren, I. B. Eisdorfer, W. E. Thompson, and J. E. Zarembo, *J. Pharm. Sci.* **55**, 144 (1966).

<sup>63</sup> M. B. Wechsler and I. S. Forrest, *J. Neurochem.* **4**, 366 (1959).

spectra has been reported by Skorodumov *et al.*<sup>64</sup>: the methyl ester of 10-methyl-3-phenothiazine carbamic acid and its sulfoxide have the same melting point and give no depression when mixed, but show characteristically distinct UV spectra.

Correlations between UV spectra and the structure of phenothiazine derivatives were investigated by Cauquil and Casadevall,<sup>65</sup> Pinyazhko and Turkevich,<sup>66</sup> Warren *et al.*,<sup>62</sup> and others.<sup>27, 67-69</sup> There are important differences between the spectra of 2- and 3-substituted derivatives. An alkyl or aminoalkyl group in position 10 affects but little the spectra of both phenothiazines and phenothiazine-5-oxides (see also Section III, A, 2), while *N*-acylation affects the spectral parameters to a greater extent. All of these spectral changes consist of shifts and variations of the intensity of the two absorption maxima characteristic of phenothiazine and its derivatives ( $\lambda_{\max}$  253 and 320  $m\mu$  for unsubstituted phenothiazine). The influence exerted by substituents like Cl,  $-\text{CF}_3$ , or alkyl, located in the benzene rings of phenothiazine, is small; that of  $-\text{NO}_2$ ,  $-\text{SO}_2$ -aryl,  $-\text{S}$ -alkyl, or  $-\text{S}$ -acyl groups is greater. A correlation between the length of the aminoalkyl side chain from position 10 and the amount of shift of the absorption maxima was also reported.<sup>62</sup>

Spectrofluorimetric studies on some phenothiazines have been reported.<sup>70</sup>

## 2. Infrared Spectra

The infrared (IR) spectra of a vast number of phenothiazine derivatives have been recorded. From the data available, some general conclusions may be drawn concerning the diagnostic value of these spectra in establishing the existence and position of various substituents on the phenothiazine ring.

<sup>64</sup> V. A. Skorodumov, N. K. Shagako, and S. V. Zhuravlev, *Zh. Obshch. Khim.* **34**, 621 (1964); *Chem. Abstr.* **60**, 13240e (1964).

<sup>65</sup> G. Cauquil and A. Casadevall, *Bull. Soc. Chim. France*, 1061 (1955).

<sup>66</sup> I. R. M. Pinyazhko and M. M. Turkevich, *Farmatsevt. Zh. (Kiev)* **19**, 44 (1964); *Chem. Abstr.* **64**, 13564e (1966).

<sup>67</sup> J. Schmitt, J. Boitard, A. Hallot, P. Comoy, M. Suquet, and J. J. Panouse, *Bull. Soc. Chim. France*, 340 (1961).

<sup>68</sup> J. J. Lafferty, E. Garvey, E. A. Nodiff, W. E. Thompson, and C. L. Zirkle, *J. Org. Chem.* **27**, 1346 (1962).

<sup>69</sup> L. K. Turner, *J. Forensic Sci.* **4**, 39 (1963).

<sup>70</sup> J. B. Ragland and V. J. Kinross-Wright, *Anal. Chem.* **36**, 1356 (1964).

The presence of a band at about  $3340\text{ cm}^{-1}$  (value of unsubstituted phenothiazine in the solid state) indicates an unsubstituted heterocyclic nitrogen.<sup>68, 71-74</sup> However, this characteristic N—H stretching vibration fails to appear in its usual form in the spectra of some 5-oxides,<sup>75</sup> being replaced by a series of bands in the  $3050\text{--}3300\text{ cm}^{-1}$  region. This is due to intermolecular associations through hydrogen bonds between the NH and SO groups of two closely disposed molecules. If substituents are present in the vicinity of the NH (positions 1 and 9) and/or SO group (positions 4 and 6), the hydrogen bonding is sterically hindered and a more or less strong band appears in the  $3340\text{ cm}^{-1}$  region, its intensity being controlled by the magnitude of the steric effects.

The bands at  $1560$  and  $1590\text{ cm}^{-1}$  assigned to the aromatic system<sup>62</sup> are very steady in location and therefore constitute a characteristic feature of the spectra of phenothiazine derivatives.

The oxidation of sulfur to the 5-oxide and 5,5-dioxide gives rise in the IR spectra to a band at  $1010\text{--}1075\text{ cm}^{-1}$  (SO stretching vibration), or to two bands, at  $1120\text{--}1160\text{ cm}^{-1}$  and  $1300\text{--}1350\text{ cm}^{-1}$  ( $\text{SO}_2$  symmetrical and asymmetrical stretching modes), which may be used in identifying these oxidation products.<sup>62, 69, 75-79</sup> The band assigned to the sulfoxide group is sometimes accompanied by another one at lower frequencies ( $976\text{ cm}^{-1}$  in phenothiazine-5-oxide), attributable to association through hydrogen bonds, which is supported by the disappearance of this band in *N*-methylphenothiazine-5-oxide.<sup>75</sup>

Extensively studied, but still very controversial, is the use of

<sup>71</sup> E. Profft and F. Kasper, *Arzneimittel-Forsch.* **12**, 48 (1962).

<sup>72</sup> G. Scapini and G. P. Gardini, *Ateneo Parmense* **35**, 328 (1964); *Chem. Abstr.* **63**, 3776a (1965).

<sup>73</sup> S. V. Zhuravlev and A. N. Gritsenko, *Khim. Geterosikl. Soedin., Akad. Nauk Latv. SSR*, 250 (1965); *Chem. Abstr.* **63**, 8348g (1965).

<sup>74</sup> G. Pappalardo, L. Amoretti, and G. P. Gardini, *Ann. Chim. (Rome)* **55**, 196 (1965); *Chem. Abstr.* **63**, 2968c (1965).

<sup>75</sup> N. A. Kudryavtseva, Z. V. Pushkareva, and V. F. Gryazev, *Khim. Geterosikl. Soedin., Akad. Nauk Latv. SSR*, 523 (1965); *Chem. Abstr.* **64**, 2867a (1966).

<sup>76</sup> H. L. Yale, F. Sowinsky, and J. Bernstein, *J. Am. Chem. Soc.* **79**, 4375 (1957).

<sup>77</sup> H. Gilman and R. O. Ranck, *J. Org. Chem.* **23**, 1903 (1958).

<sup>78</sup> K. Zehnder, F. Kalberer, W. Kreis, and J. Rutschmann, *Biochem. Pharmacol.* **11**, 535 (1962).

<sup>79</sup> C. Bodea, V. Fărcășan, and T. Panea, *Rev. Roumaine Chim.* **11**, 239 (1966).

IR spectra in determining the positions of the substituents on the benzene rings of phenothiazine. This question was first met when 3-substituted diphenylamines were subjected to thionation; two isomeric phenothiazines may be obtained in this reaction, with the substituent in position 2 or 4. It would have been expected that an unambiguous distinction could be made between these two possibilities by IR spectroscopy, inasmuch as in the case of the 2-substituted phenothiazines the benzene ring carrying the substituent is 1,2,4-trisubstituted, whereas in the 4-substituted isomer there is 1,2,3-substitution. Smith<sup>80</sup> applied this criterion in the case of 2- and 4-fluorophenothiazine, and many other authors subsequently used the out-of-plane C—H deformation vibrations as indications of the positions of the substituents.<sup>28, 68, 71, 76, 81–87</sup>

However, many phenothiazine derivatives display anomalous spectral behavior in the region 700–900  $\text{cm}^{-1}$  resulting in the appearance of unexpected bands, indicating erroneous substitution patterns that do not exist in the molecule in question,<sup>72, 88, 89</sup> and in the lack of the bands corresponding to the real structure.<sup>68</sup> It may be concluded that no structural assignment concerning the positions of substituents on the benzene rings of phenothiazine can be made using IR data only.

The bands arising from the substituents attached to the phenothiazine ring are generally normal, and useful in structural confirmation.<sup>90, 91</sup> Some interesting observations were made by Schmitt

<sup>80</sup> N. L. Smith, *J. Org. Chem.* **15**, 1125 (1950).

<sup>81</sup> J. Cymerman-Craig, W. P. Rogers, and M. E. Tate, *Australian J. Chem.* **9**, 397 (1956).

<sup>82</sup> P. N. Craig, E. A. Nodiff, J. J. Lafferty, and G. E. Ulliot, *J. Org. Chem.* **22**, 709 (1957).

<sup>83</sup> J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Guldman, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta* **41**, 1061 (1957).

<sup>84</sup> E. A. Nodiff and P. N. Craig, *J. Org. Chem.* **26**, 824 (1961).

<sup>85</sup> H. Bräuniger and K. F. Ahrend, *Arch. Pharm.* **298**, 627 (1965).

<sup>86</sup> H. Bräuniger and K. F. Ahrend, *Pharmazie* **20**, 758 (1965).

<sup>87</sup> H. Bräuniger and K. F. Ahrend, *Pharmazie* **21**, 288 (1966).

<sup>88</sup> A. Roe and W. F. Little, *J. Org. Chem.* **20**, 1577 (1955).

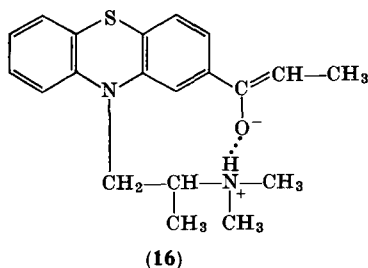
<sup>89</sup> E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *J. Org. Chem.* **25**, 60 (1960).

<sup>90</sup> S. P. Massie, I. Cooke, and W. A. Hills, *J. Org. Chem.* **21**, 1006 (1956).

<sup>91</sup> G. Cauquil, E. Casadevall, and A. Mison, *Bull. Soc. Chim. France*, 598 (1964).



*et al.*<sup>67, 92</sup> in the case of 2-keto- and 2-hydroxyalkyl phenothiazines, substituted in position 10 with dialkylaminoalkyl groups. The spatial distribution of these substituents provides favorable conditions for the formation of very strong hydrogen bonds, up to total transfer of the proton between the —OH groups—either preexisting or appearing through keto-enol tautomerism—and the tertiary nitrogen atom in the side chain (cf. 16). This leads to significant modifications of the IR spectrum.



The ion  $R_3NH^+$  combined with  $X^-$ , present in the molecule of many phenothiazine drugs, used as salts, gives rise to a broad band in the  $2300\text{--}2500\text{ cm}^{-1}$  range.<sup>62</sup>

As with UV spectra, IR spectrophotometry has also been used for analytical purposes.<sup>93, 94</sup>

A systematic survey of the IR spectra of the principal phenothiazine drugs enabled Warren *et al.*<sup>62</sup> to distinguish four typical bands in the regions  $730\text{--}755$ ,  $785\text{--}800$ ,  $840\text{--}870$ , and  $915\text{--}928\text{ cm}^{-1}$  and a characteristic "fingerprint" which may be used in the identification of these drugs.

### 3. Nuclear Magnetic Resonance Spectra

In order to clarify the problem of the position at which metabolic ring hydroxylation of phenothiazine drugs occurs, the nuclear magnetic resonance (NMR) spectra of some substituted phenothiazines were investigated.<sup>95, 96</sup> Although the application of NMR spectroscopy

<sup>92</sup> J. Schmitt, M. Suquet, M. Brunaud, and G. Callet, *Bull. Soc. Chim. France*, 1140 (1961).

<sup>93</sup> N. Oi, *Yakugaku Zasshi* **85**, 996 (1965); *Chem. Abstr.* **64**, 4870c (1966).

<sup>94</sup> T. G. Alexander and S. A. Koch, *J. Assoc. Offic. Agr. Chemists* **48**, 618 (1965).

<sup>95</sup> J. Cymerman-Craig, D. E. Green, S. K. Roy, L. H. Piette, and K. O. Loeffler, *J. Med. Chem.* **8**, 392 (1965).

<sup>96</sup> L. H. Piette, G. Bulow, and I. S. Forrest, *Psychopharmacol. Serv. Center Bull.* **2**, 46 (1962).

to the phenothiazine derivatives is still at its beginning, some important features may already be outlined.

Thus, it has been pointed out that both *N*-substitution<sup>95</sup> and oxidation to sulfoxide or sulfone<sup>62</sup> shift the signals assigned to the aromatic ring protons; in the second case, additional splittings occur. A more detailed analysis of the signals arising from ring protons enabled Cymerman-Craig *et al.*<sup>95</sup> to conclude that characteristic couplings may be attributed to each type of substitution, so that NMR may be used as a tool in determining the site of *in vivo* hydroxylation.

The use of NMR and IR spectroscopy has been recommended for the identification of phenothiazine drugs and detection of impurities in samples of such drugs,<sup>62, 94</sup> inasmuch as the substituents, and particularly the side chain, give rise to characteristic groups of signals.

#### D. OTHER PHYSICAL PROPERTIES

Tavernier and Lamouroux<sup>97</sup> determined the heat of combustion and the heat of formation of phenothiazine at constant volume and constant pressure.

Some regularities concerning the melting points of substituted phenothiazines were observed. Thus, most 2- and 3-substituted phenothiazines have melting points in the 160–200° range, while the 1 and 4 isomers melt in the 100–120° interval.<sup>81, 83, 89, 98, 99</sup> In its general lines this regularity holds also for disubstituted phenothiazines.<sup>83, 89</sup> The 2- and 3-substituted isomers are also less soluble than 1- and 4-isomers.<sup>89</sup> These differences are probably due to the geometrical shape of the molecule which allows a closer packing in the case of the derivatives substituted in positions 2 and 3 (with the substituents disposed roughly parallel to the long axis of the molecule), as compared with those carrying the substituents in 1 and 4. This gives rise to more stable crystalline lattices for the former group of derivatives.

A special procedure for obtaining high and sharp melting points of the phenothiazines has been developed.<sup>95</sup>

<sup>97</sup> P. Tavernier and M. Lamouroux, *Mem. Poudres* **39**, 335 (1957).

<sup>98</sup> S. P. Massie and P. K. Kadaba, *J. Org. Chem.* **21**, 347 (1956).

<sup>99</sup> H. Gilman and J. W. Diehl, *J. Org. Chem.* **26**, 2938 (1961).

The absolute solubilities and the partition coefficients of phenothiazine and of some of its derivatives in the systems heptane–water and cyclohexane–water have been determined.<sup>55, 57, 59</sup>

Because the biological action of phenothiazine drugs may be due, at least partly, to their interaction with cell membranes, the study of adsorptivity and surface activity of phenothiazines has been carried out by several research groups.

Scholtan<sup>100, 101</sup> observed the tendency of some phenothiazines with dialkylaminoalkyl groups at the heterocyclic nitrogen to form micels in aqueous solution, associations detectable by the cryoscopic anomalies they produce. The dimensions of the colloidal particles increase with increasing number of carbon atoms in the side chain and with the introduction of a chlorine atom in the phenothiazine ring. The effect of structural factors, solubility, and ingredients on the surface activity displayed by phenothiazine drugs was investigated<sup>102–105</sup>; it has been shown that these drugs are active at concentrations near to those required for their biological action, and that the tendency to leave an aqueous medium for a less polar environment is a characteristic of all phenothiazine derivatives used as drugs. There are also reports on the adsorptivity of phenothiazines on macromolecular compounds and on other solid adsorbents.<sup>101, 106, 107</sup>

Debye–Scherrer X-ray diffraction photographs of phenothiazine and of some phenothiazine drugs were taken for analytical purposes by the Colleter group<sup>108–111</sup> and others.<sup>47</sup> An exact knowledge of the molecular structure of phenothiazines may be useful to the under-

<sup>100</sup> W. Scholtan, *Kolloid. Z.* **142**, 84 (1955).

<sup>101</sup> W. Scholtan, *Med. Chem., Abhandl. Med. Chem. Forschungsstellen Farnefabriken Bayer* **5**, 295 (1956).

<sup>102</sup> A. Villalonga, E. Fried, and J. A. Izquierdo, *Arch. Intern. Pharmacodyn.* **130**, 260 (1961).

<sup>103</sup> P. M. Seeman and H. S. Bialy, *Biochem. Pharmacol.* **12**, 1181 (1963).

<sup>104</sup> G. Zografi and I. Zarenda, *Biochem. Pharmacol.* **15**, 591 (1966).

<sup>105</sup> G. Zografi and D. E. Ausländer, *J. Pharm. Sci.* **54**, 1313 (1965).

<sup>106</sup> D. L. Sorby and E. M. Plein, *J. Pharm. Sci.* **50**, 355 (1961).

<sup>107</sup> D. L. Sorby, E. M. Plein, and J. D. Benmaman, *J. Pharm. Sci.* **55**, 785 (1966).

<sup>108</sup> J.-C. Colleter and M. Gadret, *Bull. Soc. Pharm. Bordeaux* **98**, 182 (1959).

<sup>109</sup> J.-C. Colleter and M. Gadret, *Bull. Soc. Pharm. Bordeaux* **99**, 133 (1960).

<sup>110</sup> J.-C. Colleter and M. Gadret, *Bull. Soc. Pharm. Bordeaux* **99**, 141 (1960).

<sup>111</sup> M. Gadret and C. Bregere, *Bull. Soc. Pharm. Bordeaux* **103**, 217 (1964).

standing of their pharmacological action; a more detailed investigation in this direction, using X-ray diffraction on single crystals, was initiated by Feil *et al.*<sup>112</sup>

#### IV. Free Radicals, Cations, and Charge-Transfer Complexes within the Phenothiazine Class

##### A. GENERAL

From the very beginning of the phenothiazine chemistry, its capacity to give rise to different oxidation products, now explained in terms of a successive electron loss, was realized. The first systematic study on these topics was by Kehrmann, in the first decade of the present century. He succeeded in explaining the observed phenomena, and it has been proved by recent work that most of his statements are essentially correct. A second stage was marked by Michaelis's work, which stressed the remarkable stability of the semiquinonoid forms obtained both by oxidation of phenothiazines and by reduction of quinoneiminoid phenothiazine dyestuffs. The development of electron spin resonance (ESR) spectroscopy allowed the direct investigation of the radical species, and marked the beginning of a third era in the study of redox processes in the phenothiazine class.

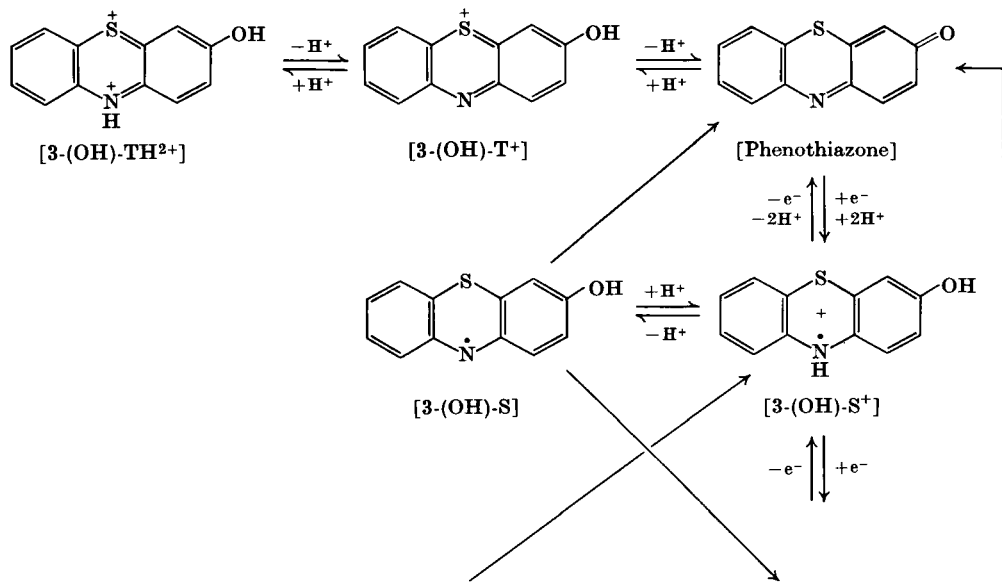
From the experimental data now available, a general view on the successive oxidation steps of phenothiazines may be outlined. The best defined are the species involved in the processes in which the first four electrons are removed, that is, between phenothiazine and phenothiazone. The subsequent oxidation stages up to thionol (7-hydroxyphenothiazone) are less extensively studied but it may be assumed that, at least in their general lines, they represent a repetition of the electronic phenomena of the first four steps.

The species one has to deal with in the oxidation of phenothiazine are the radical forms (free radicals, semiquinones, ion radicals), the oxygenated and nonoxygenated phenazathionium cations, and the nonionic oxygenated forms, like the 5-oxide, 3-hydroxyphenothiazine, and phenothiazone. These species are interrelated by redox, protolytic, and hydrolytic processes, as shown in Scheme 1.

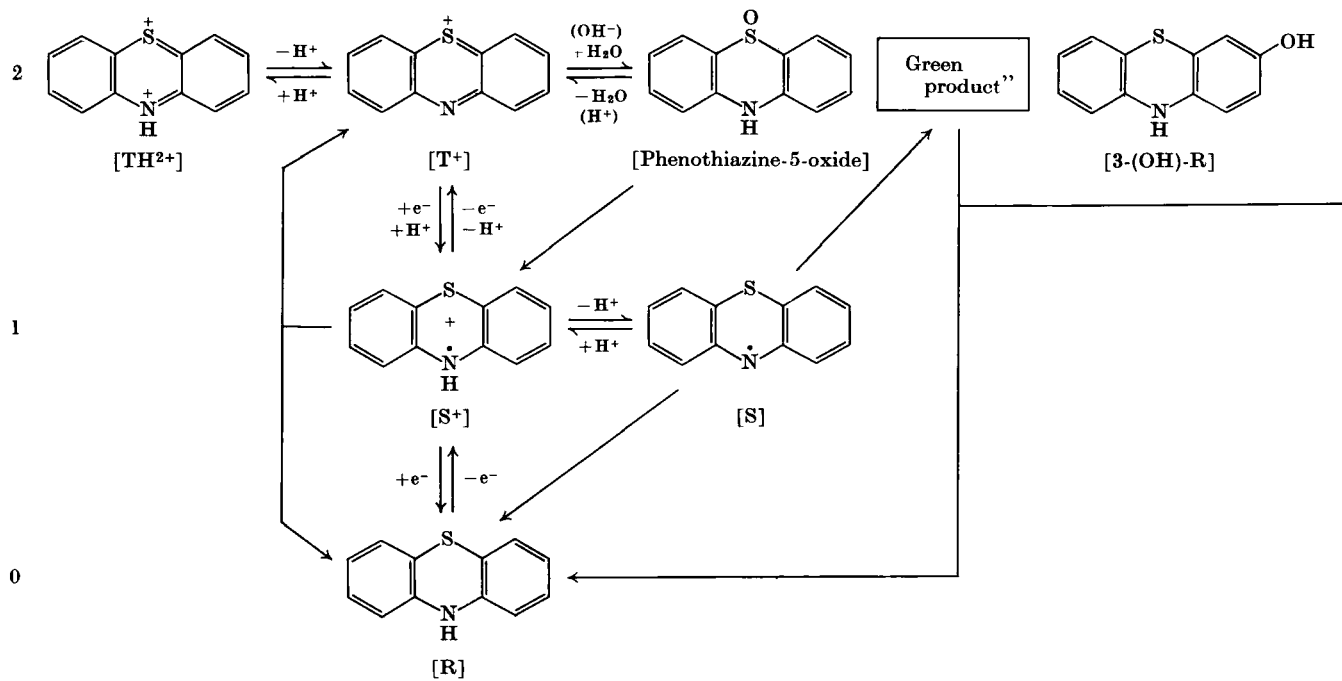
Many of the above-mentioned oxidized forms are involved in the reactions of the phenothiazine ring, primarily in the substitution

<sup>112</sup> D. Feil, M. H. Linck, and J. J. H. McDowell, *Nature* **207**, 285 (1965).

Oxidation  
degree  
4



3



SCHEME 1

reactions, but also in other chemical processes, and therefore a detailed knowledge of these species is of importance for the whole chemistry of phenothiazine.

Different notations are used in the literature to designate these species, as shown in Table I.

TABLE I  
NOTATIONS USED FOR OXIDIZED PHENOTHIAZINE SPECIES

Oxidation degree	Notations <sup>a</sup>					
0	r <sup>b</sup>	P <sup>c</sup>	R; <sup>d</sup>	Red <sup>e</sup>	R; <sup>f</sup>	R <sup>g</sup>
1	s	R	Fz <sup>+</sup>	Z	R•	S <sup>+</sup>
2	t	S	Ox <sup>2+</sup>	Ox	—	T <sup>+</sup>

<sup>a</sup> Reference by symbol in "oxidation degree 0" row applies to the whole column.

<sup>b</sup> L. Michaelis, S. Granick, and M. P. Schubert, *J. Am. Chem. Soc.* **63**, 351 (1941).

<sup>c</sup> J.-P. Billon, *Bull. Soc. Chim. France*, 1923 (1961).

<sup>d</sup> D. C. Borg and G. C. Cotzias, *Proc. Natl. Acad. Sci. U.S.A.* **48**, 643 (1962).

<sup>e</sup> J. Badoz-Lambling and D. Stojkovic, *Bull. Soc. Chim. France*, 2709 (1963).

<sup>f</sup> F. H. Merkle, C. A. Discher, and A. Felmeister, *J. Pharm. Sci.* **53**, 965 (1964); S is used by these authors to designate the 5-oxide.

<sup>g</sup> J. Cymerman-Craig and M. E. Tate, *Progr. Drug. Res.* **3**, 84 (1961); T. N. Tozer and L. Dallas Tuck, *J. Pharm. Sci.* **54**, 1169 (1965).

In the present review a notation based on that proposed by Cymerman-Craig and Tate and then by Tozer and Dallas Tuck (last column of Table I) will be used, namely R for phenothiazines, that is, for totally reduced forms of the redox systems, S<sup>+</sup> for the semiquinonoid radical forms, and T<sup>+</sup> for the totally oxidized forms, the phenazathionium cations, resulting by the the removal of an electron and a proton from S<sup>+</sup>.

Characterization of the species corresponding to different oxidation states is best performed using electrochemical methods for their generation. When chemical reagents are used, the interaction between the oxidized forms and other substances present in the system often renders the situation rather complicated; nevertheless, careful work has yielded significant results even under such conditions.

## B. OXIDATION OF UNSUBSTITUTED PHENOTHIAZINE

The species obtained upon oxidation of unsubstituted phenothiazine have been thoroughly investigated. Substantial contributions in this

direction are primarily due to the elegant work of Billon and co-workers, using electrochemical methods, and of Shine and co-workers, who obtained the oxidized forms by chemical methods.

### 1. *Electrochemical Generation of Oxidized Forms*

Billon,<sup>113</sup> using acetonitrile as a solvent, carried out the first systematic investigations on the anodic oxidation of phenothiazine

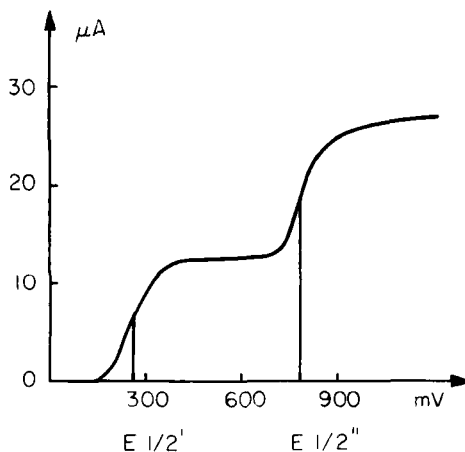


FIG. 3. Electrochemical oxidation of phenothiazine.

at a platinum electrode. The voltametric curves given by the products thus obtained clearly indicate the existence of two distinct mono-electronic oxidation stages corresponding to the following processes:



The point of inflection of the first step is found at +270 mV vs the  $Ag/Ag^+$   $10^{-2}M$  electrode and shows practically no dependence upon pH. That of the second step is located at about +750 mV; its position varies with the pH and the water content of the medium<sup>114</sup> (see Fig. 3).

<sup>113</sup> J.-P. Billon, *Bull. Soc. Chim. France*, 1784 (1960).

<sup>114</sup> J.-P. Billon, *Bull. Soc. Chim. France*, 1923 (1961).



The existence of the ion radical  $S^+$  has been directly demonstrated by ESR<sup>115,116</sup> and it has been shown that this species represents an obligatory step in the oxidation of phenothiazine to phenazathionium salts. This is a definitive confirmation of the results obtained as early as 1941 by Michaelis *et al.*<sup>117</sup> who found evidence by potentiometric titration for the stage corresponding to the removal of only one electron in the oxidation of phenothiazine with bromine or lead tetraacetate in acetic acid.

It is of importance that both the radical  $S^+$  and the totally oxidized form  $T^+$  may be quantitatively prepared on electrolysis at suitable potentials, viz. 500 and 900 mv respectively, against the  $Ag/Ag^+$   $10^{-2}$  M electrode. The solutions of  $S^+$  in acetonitrile are orange and those of  $T^+$  red. Solutions containing pure  $T^+$  give no ESR signal.<sup>115</sup> Perfect reproducibility of the processes was observed;  $S^+$  as well as  $T^+$  can be quantitatively reduced to R.

Quantitative formation of  $S^+$  is due to the net difference between the halfwave potentials of  $S^+$  and  $T^+$ , the latter appearing as a strong oxidant with respect to R, so that the reaction is a very fast



one. Consequently, the lifetime of  $T^+$  is very short as long as R is still present in the system.<sup>115</sup> The formation of a quinhydrone-type compound  $RT^+$  is thus impossible.<sup>114</sup> A coulometric titration procedure was developed for phenothiazine on this basis.<sup>118</sup>

All these phenomena result from the great stability of the  $S^+$  species, as pointed out by Michaelis. In determining this stability, an important factor is the protonation at nitrogen, which increases the number of resonance structures. The radical species decays rapidly in neutral and alkaline media, when the reverse of Reaction (3) takes place, followed by subsequent transformations of  $T^+$ .<sup>114</sup> This was confirmed by Gilbert *et al.*,<sup>119</sup> who found that on diluting the

<sup>115</sup> J.-P. Billon, G. Cauquis, J. Combrisson, and A. M. Li, *Bull. Soc. Chim. France*, 2062 (1960).

<sup>116</sup> J.-P. Billon, G. Cauquis, and J. Combrisson, *Compt. Rend.* **253**, 1593 (1961).

<sup>117</sup> L. Michaelis, S. Granick, and M. P. Schubert, *J. Am. Chem. Soc.* **63**, 351 (1941).

<sup>118</sup> J. Badoz-Lambling and D. Stojkovic, *Bull. Soc. Chim. France*, 2709 (1963).

<sup>119</sup> B. C. Gilbert, P. Hanson, R. O. C. Norman, and B. T. Sutcliffe, *Chem. Commun.*, 161 (1966).

acetonitrile solutions of  $S^+$  (prepared by chemical methods) with water buffered at pH 7 the neutral species  $S$  is formed, the lifetime of which is long enough to allow the recording of well-resolved ESR spectra; the decay of  $S$  takes place with second-order kinetics, as required by the reverse of Eq. (3) (cf., however, Section IV,G,1).

As part of a study on antioxidants the halfwave oxidation potential of phenothiazine at a wax-impregnated graphite electrode was determined and the value +239 (mv SCE) was found.<sup>120</sup>

## 2. Chemical Methods of Generation of Oxidized Forms

There are two ways of obtaining  $S^+$  and  $T^+$  by chemical methods, namely the treatment of phenothiazine with oxidants, and the conversion of phenothiazine-5-oxide into  $T^+$  salts, easily reducible to  $S^+$ . Sulfuric acid is an important reagent in both methods. The earliest work which associated the oxidation of phenothiazines with the reaction of phenothiazine-5-oxide with sulfuric acid is by Kehrmann.<sup>121, 122</sup> The existence of a radical component in the colored solutions obtained on treating phenothiazine with concentrated sulfuric acid was detected by ESR.<sup>123-126</sup> The complete elucidation of the transformations undergone by phenothiazine, phenothiazine-5-oxide, and phenothiazone on treating with acids is due to Shine and Mach.<sup>127</sup>

When phenothiazine is dissolved in concentrated sulfuric acid golden solutions are obtained which on standing become green. Here sulfuric acid acts as an oxidant which converts phenothiazine into  $S^+$ , this stage corresponding to the golden solutions; the ESR signal demonstrates that a radical is actually present. In a slow reaction,  $S^+$  is converted into the protonated phenazathionium cation,  $TH^{2+}$ , to which the green color of the aged solutions is due. This species can exist only in strongly acidic anhydrous medium because  $TH^{2+}$

<sup>120</sup> R. A. Nash, D. M. Skauen, and W. C. Purdy, *J. Am. Pharm. Assoc.* **47**, 433 (1958).

<sup>121</sup> F. Kehrmann, J. Speitel, and E. Grandmougin, *Ber. Deut. Chem. Ges.* **47**, 2976 (1914).

<sup>122</sup> F. Kehrmann and M. Sandoz, *Ber. Deut. Chem. Ges.* **50**, 1673 (1917).

<sup>123</sup> E. Crosignani, P. Franzosini, G. Siragusa, and L. Zanotti, *Bull. Ampere* **10**, Spec. Sect., 153 (1961).

<sup>124</sup> C. Lagercrantz, *Acta Chem. Scand.* **15**, 1545 (1961).

<sup>125</sup> L. Dallas Tuck and D. W. Schieser, *J. Phys. Chem.* **66**, 937 (1962).

<sup>126</sup> J.-M. Lhoste and F. Tonnard, *J. Chim. Phys.* **63**, 678 (1966).

<sup>127</sup> H. J. Shine and E. E. Mach, *J. Org. Chem.* **30**, 2130 (1965).

itself is a strong acid. The prototropic equilibrium corresponding to its dissociation is given in Eq. (4). The existence of  $\text{TH}^{2+}$  in other

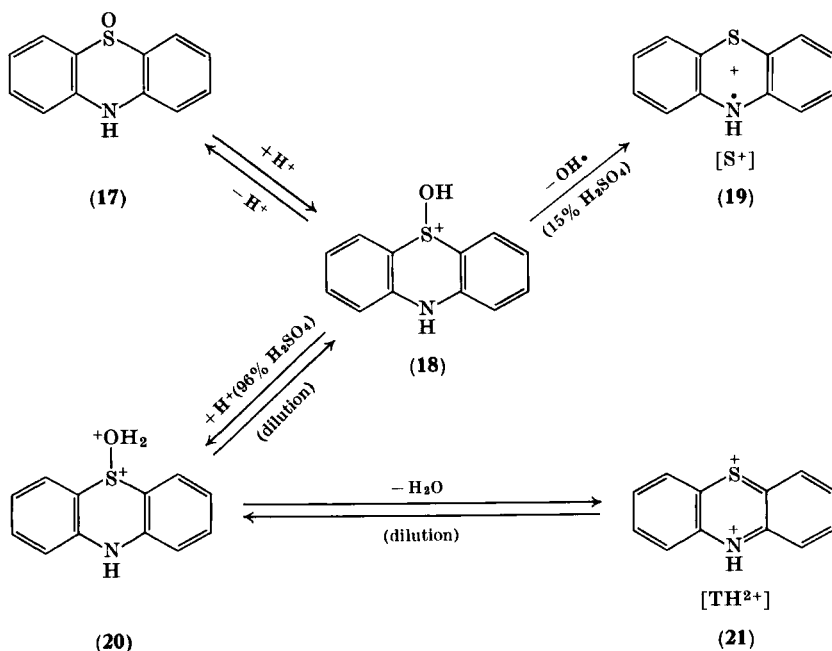


media, as claimed by some earlier authors, is very unlikely, the actual species which is present under these conditions being  $\text{T}^+$ . Equation (4) explains the dependence upon pH of the potential characterizing the second step of the electrolytic oxidation of phenothiazine (Section IV, B, 1) since the removal of an electron from  $\text{S}^+$  would lead to  $\text{TH}^{2+}$ .

It is not possible to prepare pure  $\text{T}^+$  acting with sulfuric acid on phenothiazine; solutions containing only  $\text{T}^+$  and giving no ESR signal are obtained when phenothiazine-5-oxide is dissolved in perchloric acid.<sup>114</sup> Analytical data clearly show that  $\text{T}^+$  carries only one electrical charge, the ratio between the phenothiazine moiety and the  $\text{ClO}_4^-$  anion being 1 : 1. The green sulfuric solutions of  $\text{TH}^{2+}$  (Kehrmann's "diacid holoquinonoid salt"<sup>121, 122</sup>) give, on dilution with water, brown-red solutions<sup>128</sup> which contain a mixture of different species,  $\text{T}^+$  ("monoacid holoquinonoid salt"<sup>121, 122</sup>) predominating. Further dilution leads to a solution in which  $\text{S}^+$  predominates (semi-quinonoid salt, called "meriquinonoid" by Kehrmann<sup>121, 122</sup>).

Diluting sulfuric acid solutions of phenothiazine with water one obtains solutions which are identical to those obtained by dissolving phenothiazine-5-oxide in  $\text{H}_2\text{SO}_4$  of the same concentration. In a study of the dependence of these processes upon the concentration of sulfuric acid, Shine and Mach<sup>127</sup> treated phenothiazine-5-oxide with sulfuric acid-water mixtures (Scheme 2). Protonation of phenothiazine-5-oxide (**17**) is the first step, forming **18**. The latter may be transformed following two different pathways. When diluted (15%) sulfuric acid is used, **18** yields only  $\text{S}^+$  (**19**), this process being interpreted by the authors as a homolytic cleavage, supported by the favorable influence exerted by irradiation on this reaction. At higher acid concentrations **18** undergoes a second protonation and **20** thus formed spontaneously dehydrates to  $\text{TH}^{2+}$  (**21**). This species remains as such only in very concentrated (96%) sulfuric acid. At intermediate concentrations both processes occur, the concentration of  $\text{H}_2\text{SO}_4$  determining which predominates; dehydration under these conditions leads to  $\text{T}^+$  rather than to  $\text{TH}^{2+}$ . On diluting solutions containing  $\text{TH}^{2+}$  the reverse of the dehydration process takes place,

<sup>128</sup> F. de Barry-Barnett and S. Smiles, *J. Chem. Soc.* **95**, 1253 (1909).



SCHEME 2

so that passing through  $T^+$  and the intermediates **20** and **18** one gets  $S^+$ . This explains why identical solutions may be obtained starting with phenothiazine or phenothiazine-5-oxide, as mentioned above.

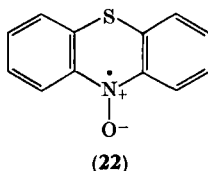
Ceric ammonium sulfate yields  $S^+$  if phenothiazine is titrated with this reagent up to the first point of equivalence. The stability of  $S^+$  thus formed was investigated at different pH<sup>129</sup> (see also Section IV, C). The ions  $Fe^{3+}$  and  $Ce^{4+}$  adsorbed on Dowex 50 also convert phenothiazine into  $S^+$ , which remains firmly attached to the resin and gives, in this state, an ESR signal similar to those of the sulfuric solutions, but with enhanced asymmetry.<sup>124</sup> At too great concentrations of  $Fe^{3+}$  the hyperfine structure of the ESR signal disappears and  $S^+$  is no longer attached to the resin phase. Phenothiazine-5-oxide displays under these conditions a similar behavior, but it is reasonable to suppose that, in this case, the strong acidity of the cation exchanger is responsible for the appearance of  $S^+$  (cf. the action of  $H_2SO_4$  on the same substance).

<sup>129</sup> Th. N. Tozer and L. Dallas Tuck, *J. Pharm. Sci.* **54**, 1169 (1965).

ESR signals identical to those of the sulfuric solutions are recorded when hydrogen peroxide acts on phenothiazine in ethanolic solutions acidulated with HCl.<sup>125</sup>

As phenothiazine is a good electron donor, there are many papers on the interaction of this compound with various acceptors (see Sections III,A,1, and IV,H,1). In most cases, authentic charge-transfer complexes are obtained; however, with very strong acceptors, e.g., 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, (DDQ), there is total transfer of one electron, leading to  $S^+$ .<sup>130</sup> It is possible that the same process accounts, at least partly, for the paramagnetism of the "phenazathionium iodide" prepared by Pummerer and Gassner<sup>131</sup> and of the "phenazathionium picrate".<sup>132</sup> (cf. however, Section IV,H,2).

Interesting results have been reported by Buchachenko<sup>133, 134</sup> who obtained the *N*-oxide of the neutral radical S (22) on treating pheno-



thiazine with hydroperoxides under special conditions. The ESR spectrum of 22 supports the *N*-oxide structure assigned to it and indicates that the spin density on nitrogen is greater than that of any other radical of the phenothiazine class.

During mechanical processing of rubber to which phenothiazine was added as an antioxidant, the oxidation of the latter to the radical was observed.<sup>135</sup>

Sodium nitrite in acid media oxidizes phenothiazine to colored

<sup>130</sup> R. Foster and P. Hanson, *Biochim. Biophys. Acta* **112**, 482 (1966).

<sup>131</sup> R. Pummerer and S. Gassner, *Ber. Deut. Chem. Ges.* **46**, 2321 (1913).

<sup>132</sup> P. Ackermann, G. Berthet, J. P. Imbaud, and A. Kergomard, *Bull. Ampere* **10**, Spec. Sect., 173 (1961).

<sup>133</sup> A. L. Buchachenko, *Opt. i Spektroskopiya* **13**, 795 (1962); *Chem. Abstr.* **58**, 5171h (1963).

<sup>134</sup> A. L. Buchachenko, "Stabil'nye Radikaly," p. 113. Izd. Akad. Nauk S.S.S.R., Moscow, 1963.

<sup>135</sup> J. Beniska, S. M. Kavun, Z. N. Tarasova, and B. A. Dogadkin, *Vysokomolekul. Soedin.* **8**, 893 (1966); *Chem. Abstr.* **65**, 5632f (1966).

products but the chemical aspects of the process are not elucidated.<sup>136-138</sup>

Photochemical oxidation of phenothiazine has also been observed.<sup>139</sup>

### 3. Physical Characterization of the Oxidized Forms

Absorption UV and visible spectroscopy have characterized the oxidized forms obtained as described above; in the case of the radical species very significant supplementary information was provided by ESR spectroscopy.

Formation of  $S^+$  is revealed by an orange coloration of the solutions when phenothiazine is electrochemically oxidized in acetonitrile and by a golden color when sulfuric acid is used as an oxidant. Characteristic absorption maxima located at 271, 437 and 515  $m\mu$  were assigned to this species.<sup>114, 127</sup> The same spectrum is recorded when equivalent quantities of phenothiazine and phenothiazine-5-oxide are dissolved in 65% perchloric acid,<sup>114, 119</sup> the sulfoxide being first converted by the acid into  $T^+$  (see Scheme 2, Section IV, B, 2), then reduced to  $S^+$  by phenothiazine (R) as shown by Eq. (3) (Section IV, B, 1).

In concentrated sulfuric acid  $S^+$  is further oxidized to  $TH^{2+}$ , and the UV spectrum changes accordingly; the bands of the latter species are found at 287 and 455  $m\mu$ .<sup>127</sup>

Another characteristic spectrum with absorption maxima at 281 and 420  $m\mu$  is displayed by solutions containing  $T^+$ , obtained either on further electrochemical oxidation<sup>114, 115</sup> or on treating phenothiazine-5-oxide with perchloric acid.<sup>114</sup>

With these spectral assignments, one is able to follow the kinetics of oxidized forms. An example is provided by the processes which take place when phenothiazine-5-oxide is dissolved in 97% formic acid.<sup>127</sup> The characteristic absorption pattern with four maxima (225, 270, 302, and 336  $m\mu$ ) of the sulfoxide may be observed for a short time. This spectrum is then replaced by that of  $T^+$ , which undergoes slow

<sup>136</sup> P. V. Kristalev, *Izv. Tomsk. Politekhn. Inst.* **102**, 160 (1959); *Chem. Abstr.* **58**, 8405b (1963).

<sup>137</sup> P. V. Kristalev, *Tr. Komis. Anal. Khim., Akad. Nauk SSSR, Inst. Geokhim. i. Analit. Khim.* **11**, 306 (1960); *Chem. Abstr.* **55**, 8153b (1961).

<sup>138</sup> B. Ozoz, *Turk Ijiyen Tecrubi Biyol. Dergisi* **24**, 293 (1964); *Chem. Abstr.* **63**, 4094c (1965).

<sup>139</sup> G. Urban and W. A. Behrendt, *Proc. 3rd Intern. Congr. Photobiol., Copenhagen, 1960* p. 591. Elsevier, Amsterdam, 1961; *Chem. Abstr.* **59**, 2316f (1963).

reduction, and the final spectrum reveals that  $S^+$  is the predominant component of the solution.

Particularly valuable for  $S^+$  are the ESR data. This method directly demonstrated the monoelectronic character of the first oxidation step, excluding the quinoxaline forms, and showed that R may be quantitatively converted into  $S^+$ . Second, since identical ESR signals were obtained in all the four cases so far mentioned—namely (i) the first step of electrochemical oxidation, (ii) the action of sulfuric acid and of other chemical oxidants, (iii) the treatment of phenothiazine-5-oxide with phenothiazine in perchloric acid, and (iv) in the other reductive processes involving  $T^+$  in acid media—it may be considered as demonstrated that  $S^+$  is formed in all these reactions. Third, the features of the ESR spectrum demonstrate that a proton is attached to the heterocyclic nitrogen, both in acid and neutral media. Hence  $S^+$ , unlike  $TH^{2+}$ , is a weak acid, and the different behavior of the two oxidation potentials corresponding to  $S^+$  and  $T^+$  is thus better understood.

In order to obtain this and other structural information from the analysis of the ESR signals, at least medium resolutions of the spectra must be achieved. Besides the usual precautions, when working with phenothiazines special attention must be paid to the removal of the totally reduced forms from the samples under investigation. It has been shown that on adding phenothiazine to a solution of  $S^+$  in acetonitrile, the hyperfine structure of the signal is entirely lost and an unresolved singlet is obtained.<sup>140</sup> This is due to electron exchange between  $S^+$  and R, proceeding at a high frequency relative to the hyperfine structure. The latter reappears when this exchange is hindered either by dilution, increasing the viscosity, or removal of phenothiazine. Bodea and Silberg reported that this hyperfine structure loss is particularly apparent when highly halogenated phenothiazines are oxidized with sulfuric acid; this reaction is incomplete even at elevated temperatures, owing to the high oxidation potentials of such phenothiazine derivatives, and the unoxidized compound which unavoidably remains causes poor resolution of the spectra<sup>141</sup> (see Section IV, C).

The presence of the  $=\dot{N}H$  group in  $S^+$  is indicated by the fact that the ESR signal at medium resolution shows a quadruplet, the result

<sup>140</sup> J.-P. Billon, G. Cauquis, and J. Combrisson, *J. Chim. Phys.* **61**, 374 (1964).

<sup>141</sup> C. Bodea and I. Silberg, *Rev. Roumaine Chim.* **10**, 887 (1965).

of an almost equal coupling of the unpaired electron with the  $N^{14}$  nucleus and the proton, as intuitively shown by Lagercrantz<sup>124</sup> (Fig. 4).

The 1:2:2:1 intensity ratio of the components of the quadruplet is evidence for this assignment. In  $D_2SO_4$  the quadruplet gives place to a triplet, because the proton attached to nitrogen is replaced by deuterium, and under conditions of medium resolution the poor

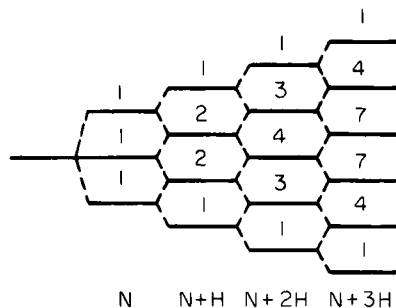


FIG. 4. Diagram of the energy level splitting. The figures give the relative intensities of the components.

coupling with deuterium (magnetic moment 1) is not observed. On diluting the sulfuric acid solutions with deuterium oxide, Lhoste and Tonnard<sup>126</sup> obtained well-resolved spectra of the *N*-deuterated  $S^+$  showing further splitting of each line of the triplet into three lines by interaction with the deutron. The side ring protons produce further splitting of the lines of the nonet.

A controversial problem is the cause of the pronounced asymmetry of some ESR spectra,<sup>124</sup> while others are symmetric or only slightly asymmetric.<sup>114</sup> At least four reasons have been suggested to explain this asymmetry. First, highly pure phenothiazine can be prepared only by using special techniques; when the radical is prepared, by chemical methods in particular, small amounts of other radicals (e.g., 3-hydroxy- $S^+$ ) may be present with the predominant species in the system. Superposition of the signals from the impurities upon the main spectrum may lead to asymmetry. Another source of asymmetry may be the so-called asymmetrical broadening, due to the dependence of the line width on the value of  $I_z$  (the projection of the nuclear spin on the direction of the magnetic field).<sup>142</sup> If this

<sup>142</sup> A. L. Buchachenko, "Stabil'nye Radikaly," pp. 26 and 115. Izd. Akad. Nauk S.S.S.R., Moscow, 1963.



cause were always to operate, symmetrical spectra would be excluded; however, Billon *et al.*<sup>140</sup> reported perfectly symmetrical ESR spectra from acetonitrile solutions of  $S^+$ . The fact that the same authors also obtained unsymmetrical spectra in sulfuric acid solutions, confirming earlier literature data,<sup>143</sup> underlines the part played by the solvent in the asymmetry. Two properties of the solvent are mainly involved here, the viscosity and the dielectric constant. The existence, in the molecule of phenothiazine of a sulfur atom, which possesses a relatively pronounced spin-orbit coupling, entails  $g$  factor anisotropy, which becomes manifest when random orientation of the molecules is hindered by the high viscosity of the solvent. This would explain the experimental observation that in concentrated sulfuric acid solutions highly asymmetrical spectra are recorded, this asymmetry diminishing on dilution,<sup>127</sup> and that the signals given by  $S^+$  in the adsorbed state are particularly unsymmetrical.<sup>124</sup> On the other hand, in acetonitrile, a solvent with low viscosity, symmetrical spectra are found.<sup>140</sup> This explanation does not account, in exchange, for the asymmetry of the spectra taken in aromatic hydrocarbons like toluene and xylene.<sup>142</sup> Finally, phase shift of the radio wave at the air-solvent interface as a possible cause of the asymmetry was experimentally demonstrated by Blois *et al.*<sup>144</sup> for diphenylpicrylhydrazyl (DPPH) and other radicals. In order for this factor to be effective, a relatively high dielectric constant of the solvent is required, so that this explanation is valid for the asymmetry of the spectra in sulfuric acid but not for the asymmetry of those obtained in acetonitrile (dielectric constant 37), and by no means for the asymmetry reported for hydrocarbon solutions.

It may be concluded that the alternative action of several effects accounts for the asymmetry of the ESR spectra in different cases, rather than a single common cause.

Coupling constants specially helped to elucidate the structure of  $S^+$ . As already mentioned, ESR spectra of  $S^+$  at medium resolution consist of a quadruplet. The experimental distances separating the components vary between 7.5<sup>116</sup> and 7.1 G.<sup>125, 141</sup> There is even greater lack in agreement over the coupling constants assigned to N and H of the

<sup>143</sup> D. Gagnaire, H. Lemaire, A. Rassat, and P. Servoz-Gavin, *Compt. Rend.* **255**, 1441 (1962).

<sup>144</sup> M. S. Blois, Jr., H. W. Brown, and J. E. Maling, in "Free Radicals in Biological Systems" (M. S. Blois, Jr., *et al.*, eds.), p. 117. Academic Press, New York, 1961.

NH group. However, these values vary about 7.0 G for  $a^N$  and 7.5 G for  $a^H$ , and clearly show the significant localization of the unpaired spin at the NH group. Comparison with phenoxazine indicates the influence of the electronegativity of the second heteroatom—the oxygen increasing the localization of the unpaired electron on the central ring.

TABLE II  
COUPLING CONSTANTS AND SPIN DENSITIES DERIVED FROM THE ESR  
SPECTRA OF  $S^+$  AND S

Assignment	Coupling constants, for $S^+$ (G)		Spin densities <sup>a,c</sup> for $S^+$ (%)	Coupling constants <sup>b</sup> for S (G)
	Lhoste <sup>a</sup>	Gilbert <sup>b</sup>		
$a^N$	6.52	6.52	20.9	7.06
$a_{NH}^H$	7.32	7.36	—	—
$a_{3,7}^H$	2.58	2.58	10.7	3.64
$a_{1,9}^H$	1.29	1.23	5.3	2.68
$a_{2,8}^H$	0.46	0.46	1.9	1.00
$a_{4,6}^H$	0.40	0.46	1.7	0.73

<sup>a</sup> J. M. Lhoste and F. Tonnard, *J. Chim. Phys.* **63**, 678 (1966).

<sup>b</sup> B. C. Gilbert, P. Hanson, R. O. C. Norman, and B. T. Sutcliffe, *Chem. Commun.*, 161 (1966).

<sup>c</sup> Values quoted refer only to one atom of the given kind.

Gagnaire *et al.*<sup>143</sup> first obtained resolved ESR spectra showing hyperfine splittings due to the protons of the side rings. Resolution of the contributions of all the protons was achieved by Billon *et al.*<sup>140</sup> and more recently by Gilbert *et al.*<sup>119</sup> and Lhoste and Tonnard.<sup>126</sup> Unlike the earlier work,<sup>145</sup> good agreement was obtained between the experimental spectra and those simulated on electronic computers, using the coupling constants given in Table II.

The work of Gilbert *et al.*<sup>119</sup> is of particular importance because they determined coupling constants for the uncharged phenothiazinyl free radical S.

The spin densities derived from these coupling constants agree with those calculated using the Hückel approximation. It is interesting to note that the order in which these spin densities decrease is the same as that observed in a comparison of the reactivity of the different

<sup>145</sup> S. Odiet and F. Tonnard, *J. Chim. Phys.* **61**, 382 (1964).

positions on the benzenoid side rings toward electrophilic reagents (see Section V, A).

Another incompletely elucidated problem is that of the configuration of the free radicals S and S<sup>+</sup>. Malrieu and Pullman<sup>44</sup> stated that S<sup>+</sup> is "tetragonally folded" and adopts the configuration "H-intra" (see Section III, A, 2); the nonplanarity of the radical has been claimed<sup>145</sup> as a possible cause of the disagreement between calculated and experimental ESR spectra. However, Lhoste and Tonnard,<sup>126</sup> though considering that no definitive conclusion may be drawn in this question, appear to favor the hypothesis that the radical is nearly planar. Preliminary data about the phosphorescent triplet state of the phenothiazine molecule<sup>146</sup> support this view.

### C. OXIDATION OF C-SUBSTITUTED PHENOTHIAZINES

Oxidized forms corresponding to S<sup>+</sup> and T<sup>+</sup> species may also be obtained from C-substituted phenothiazines by electrochemical and chemical methods. The oxidation products derived from 3-hydroxyphenothiazine are not discussed here; they will be dealt with in Section IV, F.

A series of C-substituted phenothiazines have been electrochemically oxidized,<sup>116, 126, 147</sup> and correlations between substituents and redox-potential values established.<sup>58</sup> The reagents used in chemical oxidations are the same as for unsubstituted phenothiazine.

The existence of a correlation between anthelmintic activity and redox potentials of phenothiazine derivatives<sup>148, 149</sup> stimulated extensive work on oxidation of C-substituted phenothiazines, and some results are presented in Table III.

These data illustrate the pronounced dependence of redox potentials upon the nature and position of the substituents. The sensitivity of phenothiazine derivatives toward oxidants corresponds in general lines to the redox potentials. Thus, as long ago as 1957 Schmitt *et al.*<sup>150</sup> reported that introduction of an acyl residue in position 2 markedly increases the resistance to oxidation—a fact of importance in

<sup>146</sup> J. M. Lhoste, A. Haug, and M. Ptak, *J. Chem. Phys.* **44**, 648 (1966).

<sup>147</sup> J.-P. Billon, *Ann. Chim. (Paris)* [13] **7**, 183 (1962).

<sup>148</sup> J. Cymerman-Craig, M. E. Tate, G. P. Warwick, and W. P. Rogers, *J. Med. Pharm. Chem.* **2**, 659 (1960).

<sup>149</sup> J. Cymerman-Craig and M. E. Tate, *Progr. Drug Res.* **3**, 84 (1961).

<sup>150</sup> J. Schmitt, J. Boitard, P. Comoy, A. Hallot, and M. Suquet, *Bull. Soc. Chim. France*, 938 (1957).

preparing drugs with improved stability. In contrast, 3,7-dimethylphenothiazine is directly oxidized by sulfuric acid to the second stage, 3,7-dimethyl-T<sup>+</sup>.<sup>127</sup>

TABLE III  
OXIDATION POTENTIALS OF C-SUBSTITUTED PHENOTHIAZINES<sup>a</sup>

Compound	Oxidation potential (mV)
Methylene blue	355
Thionine	378
3-Aminophenothiazine	451
3,7-Dimethoxyphenothiazine	475
3-Ethoxyphenothiazine	580
3-Methoxyphenothiazine	590
3,7-Dimethylphenothiazine	590
3-Methylphenothiazine	651
2-Chloro-7-methoxyphenothiazine	662
4-Chloro-7-methoxyphenothiazine	668
3-Phenylphenothiazine	679
1-Ethoxyphenothiazine	692
Phenothiazine	696
1-Methoxyphenothiazine	698
3-Fluorophenothiazine	722
3-Iodophenothiazine	758
3-Chlorophenothiazine	763
3-Bromophenothiazine	766
2-Chlorophenothiazine	776
Phenothiazine-5-oxide	~ 800
3-Nitrophenothiazine	~ 900
Phenothiazine-5,5-dioxide	~ 900

<sup>a</sup> J. Cymerman-Craig and M. E. Tate, *Progr. Drug Res.* **3**, 84 (1961).

The process of the oxidation with chemical agents is also strongly influenced by the substituent. From this aspect, Cymerman-Craig<sup>151</sup> distinguishes the following four groups of phenothiazine derivatives:

- (i) derivatives resembling methylene blue, which are oxidized in a single step to the doubly oxidized stage, the formation of semiquinone being hardly observed;

<sup>151</sup> J. Cymerman-Craig, *Psychopharmacol. Serv. Center Bull.* **2**, 44 (1962).

- (ii) 3-iodophenothiazine types, comprising derivatives in which only 50% of the monovalent oxidation step is stable; the semiquinone begins to be further oxidized when its concentration becomes greater than that of the initial compound;
- (iii) compounds showing an oxidation behavior similar to that of unsubstituted phenothiazine; two monoelectronic steps may be observed and the concentration of semiquinone in the system can significantly exceed 50%;
- (iv) compounds carrying substituents which may contribute by supplementary resonance to the stability of the semiquinone (e.g., 3-methoxyphenothiazine), the two oxidation steps being quite distinct.

The part played by the position of the substituent is illustrated by comparison of the redox potentials of 1-alkoxy- and 3-alkoxyphenothiazines; the latter are more easily oxidized. In turn, whereas 1-alkoxy derivatives show the behavior characteristic of 3-iodophenothiazine, the 3-alkoxy derivatives (group *iv* compounds) give very stable semiquinones. Obviously, *o*-quinonoid systems are, in the case of phenothiazines too, less stable than *p*-quinonoid.

A systematic survey of the influence exerted by the substituents upon the stability of semiquinone forms was undertaken by Tozer and Dallas Tuck,<sup>129</sup> in order to investigate the effect of the substituent upon the biological activity of phenothiazine derivatives, an activity correlated by many authors with *in vivo* formation of radical species. If the disproportionation reaction shown in Eq. (3) (Section IV, B, 1) were to reach equilibrium, the value  $K$  defined in Eq. (5) would express the stability of substituted  $S^+$  species.

$$K = \frac{[S^+]^2}{[R][T^+][H^+]} \quad (5)$$

Inasmuch as  $T^+$  continuously disappears from the system, being consumed in an "acid-irreversible hydrolysis," as shown in Section IV, G, it is not possible to derive  $K$  from  $S^+$  concentration measurements. Therefore, the comparison was restricted to the rate constants of semiquinone decay. This reaction has second-order kinetics and the rate constants may be correlated with the influence of the substituents (see also Section IV, D).

Phenazathionium salts have also been obtained, as in the case of unsubstituted phenothiazine, on treating the corresponding 5-oxides

with strong acids: Cymerman-Craig *et al.*<sup>152</sup> obtained 3-chlorophenazathionium chloride in the solid state (which is particularly remarkable).

Physicochemical characterization of the oxidized species was primarily made working with chemically generated ones. Usually, only parameters characterizing the main absorption maximum of the colored products obtained by the action of sulfuric acid were reported. In the case of halogenated phenothiazines, systematic determinations were carried out by Rupprecht<sup>153</sup> and the dependence of the position of the absorption maximum upon the amount and nature of the halogen atoms may be obtained from the data in Table IV.

TABLE IV  
ABSORPTION MAXIMA OF SULFURIC ACID SOLUTIONS OF HALOGENATED  
S<sup>+</sup> SPECIES

Compound	Absorption maxima $\lambda_{\max}$ , (m $\mu$ )
Phenothiazine	520
3,7-Dichlorophenothiazine	569
3,7-Dibromophenothiazine	573
1,3,7,9-Tetrachlorophenothiazine	596
1,3,7,9-Tetrabromophenothiazine	613
1,2,3,4,6,7,8,9-Octachlorophenothiazine	606
1,2,3,4,6,7,8,9-Octabromophenothiazine	640

Spectroscopic studies on *C*-substituted S<sup>+</sup> species obtained by oxidation with H<sub>2</sub>SO<sub>4</sub> have been undertaken by Beckett and Curry.<sup>58</sup> The UV and visible spectra showed that 3,7-dimethylphenothiazine is oxidized by strong electron acceptors to the corresponding S<sup>+</sup> species.<sup>130</sup>

ESR spectra of S<sup>+</sup> species obtained from 2- and 3-methyl- and 3,7-dimethylphenothiazine on electrochemical oxidation have been recorded,<sup>116, 126, 147</sup> but the interpretation of these spectra by means of the Hückel method gave no satisfactory results.<sup>126, 140, 145</sup> Well-resolved spectra of 3-methoxy- and 2-chloro-7-methoxy-S<sup>+</sup> have also been reported.<sup>96</sup>

The influence of the halogens on the ESR spectra of halogenated

<sup>152</sup> J. Cymerman-Craig, M. E. Tate, F. W. Donovan, and W. P. Rogers, *J. Med. Pharm. Chem.* **2**, 669 (1960).

<sup>153</sup> E. Rupprecht, Ph.D. Dissertation, University of München (1955).

$S^+$ , obtained on treatment of di-, tetra-, and octachloro- and -bromophenothiazines with sulfuric acid was investigated by Bodea and Silberg.<sup>141</sup> Precise  $g$  value measurements revealed a stepwise diminution of the relative influence of the halogen atoms on the ESR signal with increasing number of halogens. This was explained on the basis of the parallelism existing between the reactivity of different

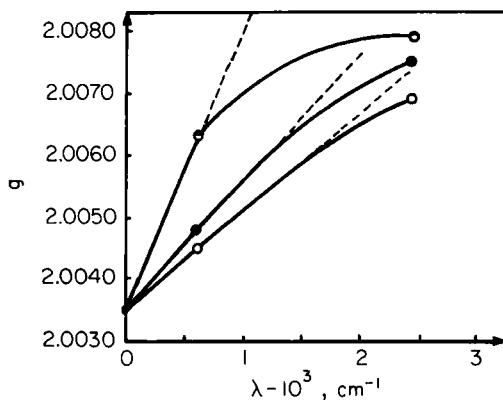


FIG. 5. Dependence of  $g$  values upon the spin-orbit coupling parameter  $\lambda$  of the halogen, in halogenated phenothiazinyls.

positions in the molecule of phenothiazine toward electrophilic reagents and the spin densities on the same positions of the phenothiazinyl radicals. The last halogen atoms, which enter the molecule with difficulty, find low spin densities in the corresponding positions. As clearly shown in Fig. 5, with increasing number of halogens there is more and more marked deviation from the linearity of the curves representing the dependence of  $g$  value upon the spin-orbit coupling parameter,  $\lambda$ .

#### D. OXIDATION OF *N*- AND *N,C*-SUBSTITUTED PHENOTHIAZINES

With the exception of *N*-methylphenothiazine, which owing to its availability served as a model substance, almost all of the investigated *N*-substituted derivatives are phenothiazine drugs; particular attention was paid to chlorpromazine. Concordant results have been obtained in the comprehensive works of Billon<sup>147</sup> through electrolytic oxidation in acetonitrile, and of Kabasakalian and McGlotten<sup>153a</sup> on polarographic oxidation at a rotating gold electrode.

<sup>153a</sup> P. Kabasakalian and J. McGlotten, *Anal. Chem.* **31**, 431 (1959).

A striking fact resulting from these studies is that oxidation is rendered more difficult by substitution at nitrogen. In the case of *N*-acylation this would be normal behavior, but with alkyl groups in position 10 it appears surprising, especially because substitution with alkyl groups at carbon atoms leads, as usual, to easier oxidation. The explanation is furnished, as shown in Section III, A, 2, by a steric

TABLE V  
INFLUENCE OF *N*-SUBSTITUTION ON THE HALFWAVE POTENTIAL OF  
PHENOTHIAZINES ON POLAROGRAPHIC OXIDATION

Substituent in position 2	Substituent in position 10	
	H	3-(4- $\beta$ -Hydroxyethyl- 1-piperazinylpropyl)
H	0.306 <sup>a</sup>	0.540 <sup>a</sup>
Cl	0.354	0.619
COCH <sub>3</sub>	0.372	0.660
CF <sub>3</sub>	0.373	0.714

<sup>a</sup> Potentials are given in volts vs NCE; data from P. Kabasakalian and J. McGlotten, *Anal. Chem.* **31**, 431 (1959).

effect, the bulky substituent in position 10 forcing the molecule to adopt the "H-extra" configuration. The influence of the substituent at nitrogen is illustrated by the redox potentials for the first oxidation step, given in Table V.

In phenothiazine drugs, the influence of the second nitrogen atom (in the dialkylaminoalkyl side chain) is also to be taken into account, the number of carbon atoms between the two nitrogens being of particular importance (cf. Section VI, A). The latter feature may be illustrated by the dependence of redox potential upon pH: when there are three carbon atoms between the nitrogens, the redox potential shows almost no variation with pH, whereas with the derivatives with only two carbon atoms the potential decreases with decreasing acidity of the medium. Variations in the degree of protonation of the exocyclic nitrogen modify its (time-average) electron-withdrawing inductive effect; the inductive effect is transmitted to the ring to different extents if chains of two or three carbon atoms are present. The attenuation effect also explains the overall easier metabolic oxidation of the drugs with a three carbon side chain



as compared with the similar derivatives having only two carbon atoms, since at physiological pH all of these drugs are in the form of salts (see Table VI).

The influence of acidity upon the stability of *N*-substituted  $S^+$  species was investigated by polarography. In 1*N* sulfuric acid, Merkle and Discher<sup>154</sup> obtained single anodic waves, while in 12*N*  $H_2SO_4$  two distinct waves were recorded. 10-Methylphenothiazine

TABLE VI  
DEPENDENCE OF HALF-WAVE POTENTIALS UPON SIDE CHAIN LENGTH

Substituent in position 10	Type of substituent	Potential V vs NCE <sup>a</sup>
3-Dimethylaminopropyl	N—C <sub>3</sub> —N	0.473
3-(4-β-Hydroxyethyl-1-piperazinyl)propyl		0.482
(1-Methyl-3-piperidyl)methyl		0.503
2-(1-Pyrrolidinyl)ethyl	N—C <sub>2</sub> —N	0.567
2-Dimethylaminopropyl		0.619
2-Diethylaminopropyl		0.620

<sup>a</sup> P. Kabasakalian and J. McGlotten, *Anal. Chem.* **31**, 431 (1959).

resembles unsubstituted phenothiazine in its oxidation behavior (see Section IV, C) giving two separate oxidation steps.<sup>151</sup> The stabilizing effect of the acidity was also noted by Tozer and Dallas Tuck.<sup>129</sup>

Merkle and Discher<sup>154</sup> prepared quantitatively, by fixed-potential electrolytic oxidation, the *N,C*-substituted  $S^+$  species from seven phenothiazine drugs. Piette *et al.*<sup>155, 156</sup> recorded the ESR spectra of such species derived from chlorpromazine and of some of its analogs, the oxidation being performed electrochemically directly in the resonant cavity.

At higher potentials oxidation leads to the 5-oxides, which appear on hydrolysis of cationic species formed by the removal of two electrons. The presence of a substituent in position 10 does not allow the removal of a positive charge by elimination of a proton, as in the case of the process described by Eq. (2) (Section IV, B, 1), and the

<sup>154</sup> F. H. Merkle and C. A. Discher, *Anal. Chem.* **36**, 1639 (1964).

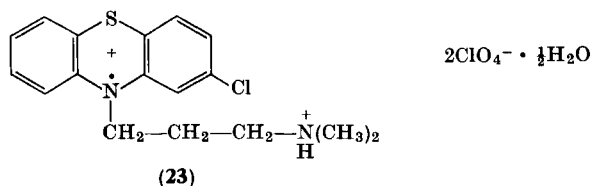
<sup>155</sup> L. H. Piette, P. Ludwig, and R. N. Adams, *J. Am. Chem. Soc.* **83**, 3909 (1961).

<sup>156</sup> L. H. Piette, P. Ludwig, and R. N. Adams, *Anal. Chem.* **34**, 916 (1962).

two electron oxidation yields a very reactive bivalent cation. Traces of water in acetonitrile suffice to hydrolyze such cations with formation of the sulfoxide.<sup>147</sup> Only with 3,7,10-trimethylphenothiazine are there indications that the bivalent cation may be directly observed.<sup>147</sup>

There are many papers on chemical and photochemical oxidation of chlorpromazine and of other drugs of this series.

Merkle *et al.*<sup>157</sup> prepared a solid perchlorate of the chlorpromazine free radical (23) by treatment of chlorpromazine-5-oxide with 70%



HClO<sub>4</sub>. The radical character was demonstrated by ESR. Its UV and visible spectra in solutions are identical to those of sulfuric acid solutions of chlorpromazine, which ESR showed to contain radical species.

Lagercrantz<sup>124</sup> obtained ESR signals from sulfuric acid solutions of a series of *N*-substituted phenothiazines. Practically identical spectra were recorded when the same substances were adsorbed on Dowex 50 activated with Fe<sup>3+</sup>. *N*-Methylphenothiazine dissolved in either H<sub>2</sub>SO<sub>4</sub> or D<sub>2</sub>SO<sub>4</sub> displays an ESR spectrum consisting in a sextet with the relative intensities of the lines 1 : 4 : 7 : 7 : 4 : 1, reflecting the almost equal interaction of the odd electron with the nitrogen and the three protons of the methyl group (see Fig. 4, Section IV, B, 3). Similar results and interpretations have been presented by many other authors, working on *N*-methyl-S<sup>+</sup> obtained by various chemical and electrochemical procedures.<sup>116, 123, 126, 140, 145</sup> The values  $a^N = 7.60$  G and  $a_{\text{NCH}_3}^H = 7.20$  G are given by Lhoste and Tonnard,<sup>126</sup> who obtained the best resolutions of these spectra.

The mechanism of the interaction between the unpaired electron and the protons of the methyl group is rather controversial; most authors believe that hyperconjugation occurs. This interpretation led to a satisfactory agreement between spin densities derived from ESR spectra and those calculated using the Hückel approximation, but other authors state that planarity of the molecule is required

<sup>157</sup> F. H. Merkle, C. A. Discher, and A. Felmeister, *J. Pharm. Sci.* **53**, 965 (1964).

for hyperconjugation to operate—a fact contrasting with the data presented in Section III, A, 2 (see however Section IV, B, 3).

In derivatives carrying longer side chains at position 10, there is less marked evidence in the ESR spectra of interaction between the unpaired electron and the protons of the side chain. Good resolution was generally more difficult to achieve with such derivatives; when it was attained, as by the Piette group,<sup>95, 155, 156, 158</sup> the triplet hyperfine structure demonstrated the predominant contribution of nitrogen. Some oxidative degradations of the side chain by the sulfuric acid and other agents were also followed and interpreted using the ESR spectra of the resulting radical species, as shown in Section VI, A.

ESR spectra of the radicals prepared by treating some drugs of the chlorpromazine series, like trifluoperazine, prochlorperazine, and others,<sup>143, 158–160</sup> with  $\text{H}_2\text{SO}_4$  have been recorded. The nature of the substituent in position 10 influences the  $g$  factors to a small extent.<sup>161</sup> The ESR signals of the different radicals have characteristic forms and may be used in identifying the drugs.

Sulfuric acid was often used, either alone or in conjunction with other oxidants such as ferric salts, to convert phenothiazine drugs and their metabolization products into the colored radical species, which may then be identified and estimated by spectrophotometry.<sup>58, 162–170</sup> Rieder<sup>167</sup> found the absorption maximum of the

<sup>158</sup> L. H. Piette and I. S. Forrest, *Biochim. Biophys. Acta* **57**, 419 (1962).

<sup>159</sup> D. C. Borg and G. C. Cotzias, *Proc. Natl. Acad. Sci. U.S.* **48**, 623 (1962).

<sup>160</sup> P. Machmer, *Z. Naturforsch.* **21b**, 934 (1966).

<sup>161</sup> D. W. Schieser and L. Dallas Tuck, *J. Pharm. Sci.* **51**, 694 (1962).

<sup>162</sup> P. Dubost and S. Pascal, *Ann. Pharm. Franc.* **11**, 615 (1953).

<sup>163</sup> D. Sasaki, *Nippon Yakurigaku Zasshi* **52**, 540 (1956); *Chem. Abstr.* **51**, 14987f (1957).

<sup>164</sup> H. Leach and W. R. C. Crimmin, *J. Clin. Pathol.* **9**, 164 (1956).

<sup>165</sup> T. Nakagawa, T. Kubota, and H. Miyazaki, *Ann. Rept. Shionogi Res. Lab.* **7**, 19 (1957); *Chem. Abstr.* **51**, 15279i (1957).

<sup>166</sup> I. S. Forrest, F. M. Forrest, and A. A. Mason, *Am. J. Psychiat.* **116**, 928 (1960).

<sup>167</sup> H. P. Rieder, *Med. Exptl.* **3**, 353 (1960).

<sup>168</sup> H. V. Street, *Chem. & Ind. (London)*, 1501 (1962).

<sup>169</sup> I. S. Forrest, M. B. Wechsler, and J. E. Sperco, *Am. J. Psychiat.* **120**, 44 (1963).

<sup>170</sup> G. H. W. Lucas and C. Fabierkiewicz, *J. Forensic Sci.* **8**, 462 (1963).

*N*-derivatives unsubstituted in position 2 at 510–514  $m\mu$ . Bathochromic shifts, up to 130  $m\mu$  in the case of  $-\text{SCH}_3$ , are observed when a substituent is introduced in position 2. The same *N,C*-substituted  $\text{S}^+$  species present in sulfuric acid solutions of chlorpromazine and chlorpromazine-5-oxide accounts for the identical UV spectra of the two solutions.<sup>168</sup> This has led to confusion in quantitative estimation of chlorpromazine metabolites extracted from tissues.

Another type of analytical application of sulfuric acid oxidation has been developed recently, based on the intense fluorescence which appears when the sulfuric solutions containing oxidized phenothiazine derivatives are diluted with dimethyl sulfoxide. It has been shown that concentrations as low as 0.01  $\mu\text{g/ml}$  may be detected this way and that substituents in position 2 decrease the intensity of the fluorescence to a greater extent than side chains at position 10.<sup>171</sup>

The formation of colored products by the action of a variety of oxidating agents has been used for the detection and assay of phenothiazine derivatives.<sup>172–177</sup> The use of chlorpromazine as an indicator in redox titrations has been recommended because of the intense color easily obtained from this substance on oxidation.<sup>178–181</sup>

Oxidizing agents with metallic cations in higher oxidation states are of interest for the titrimetric estimation of phenothiazine drugs; at the same time, there are indications of an interaction existing *in vivo* between phenothiazines and trace elements. Both these reasons have stimulated research work on the oxidation of phenothiazines

<sup>171</sup> E. Adonai Martin, *Can. J. Chem.* **44**, 1783 (1966).

<sup>172</sup> C. Fossoul, *J. Pharm. Belg.* [N.S.] **6**, 383 (1951).

<sup>173</sup> L. Cavatorta, *J. Pharm. Pharmacol.* **11**, 49 (1959).

<sup>174</sup> T. L. Flanagan, T. H. Lin, W. J. Novick, I. M. Rondish, C. A. Borchers, and E. J. van Loon, *J. Med. Pharm. Chem.* **1**, 263 (1959).

<sup>175</sup> J. H. Heyman, B. Bayne, and S. Merlis, *Am. J. Psychiat.* **116**, 1108 (1960).

<sup>176</sup> H. P. Rieder and M. Böhmer, *Helv. Chim. Acta* **43**, 638 (1960).

<sup>177</sup> H. Beral, L. Murea, M. Madgearu, E. Cuciureanu, and B. Wermescher, *Pharm. Zentralhalle* **104**, 231 (1965).

<sup>178</sup> Lee Kum-Tatt, *Anal. Chim. Acta* **26**, 285 (1962).

<sup>179</sup> Lee Kum-Tatt, *Anal. Chim. Acta* **26**, 478 (1962).

<sup>180</sup> Lee Kum-Tatt, *Anal. Chim. Acta* **26**, 583 (1962).

<sup>181</sup> H. Sanke Gowda and R. Shakunthala, *Talanta* **13**, 1375 (1966).

with reagents like lead tetraacetate,<sup>182</sup> ceric sulfate,<sup>183-185</sup> ferric salts,<sup>186</sup> and  $\text{Mn}^{2+}$  under aerobic conditions.<sup>159, 187, 188</sup>

The potentiometric titration of chlorpromazine, promethazine, and deparkine with lead tetraacetate discloses two distinct oxidation steps: the first produces a red color; in the second stage decolorization occurs. These phenomena were interpreted as the successive loss of two electrons.<sup>182</sup>

Preparation of radical species on treatment of 2,10-disubstituted phenothiazines and of other *N*-substituted derivatives of phenothiazine with equivalent amounts of  $\text{Ce}^{4+}$  salts was reported by some authors.<sup>129, 158, 187, 189</sup>

Since phenothiazine drugs inhibit the action of the enzymes involved in oxidative phosphorylation, enzymes which are activated by  $\text{Mn}^{2+}$ , Borg and Cotzias<sup>159, 187, 188</sup> undertook a study of the *in vitro* interaction between phenothiazines and manganous salts. The latter show no action on the drugs—represented in most of the experiments discussed here by chlorpromazine—but, when the medium is rendered alkaline and then back-titrated with acids in the presence of atmospheric oxygen, a red color appears. This phenomenon was carefully investigated and the authors concluded that under these conditions the ion  $\text{Mn}^{3+}$  is formed, which, despite its very low concentration and short lifetime, is able to oxidize chlorpromazine. The red product was demonstrated to be the corresponding *N,C*-substituted  $\text{S}^+$ . The close approach of the metallic cation to the molecule of the drug, necessary for the redox process to succeed, is assisted by the neutralization, in the alkaline medium, of the positive charge of the exocyclic nitrogen. It is interesting to note that the

<sup>182</sup> A. Berka, V. Prochazkova, and J. Zyka, *Cesk. Farm.* **13**, 121 (1964); *Chem. Abstr.* **61**, 12640a (1964).

<sup>183</sup> H. Beral, L. Murea, M. Madgearu, and E. Cuciureanu, *Acta Pharm. Jugoslav.* **15**, 77 (1965).

<sup>184</sup> L. Murea, H. Beral, E. Cuciureanu, and M. Madgearu, *Rev. Chim. (Bucharest)* **16**, 600 (1965); *Chem. Abstr.* **64**, 14031e (1966).

<sup>185</sup> J. Blazek, *Cesk. Farm.* **15**, 200 (1966); *Chem. Abstr.* **65**, 8677h (1966).

<sup>186</sup> I. Gordon Fels and M. Kaufman, *Nature* **183**, 1392 (1959).

<sup>187</sup> D. C. Borg and G. C. Cotzias, *Proc. Natl. Acad. Sci. U.S.* **48**, 617 (1962).

<sup>188</sup> D. C. Borg and G. C. Cotzias, *Proc. Natl. Acad. Sci. U.S.* **48**, 643 (1962).

<sup>189</sup> G. Dushinsky and O. Lishkova, *Chem. Zvesti* **12**, 213 (1958); *Chem. Abstr.* **52**, 12681f (1958).

decay of the radical species obeys second-order kinetics, as required for a dismutation process.

Photochemical oxidation of phenothiazine derivatives is a problem of great practical importance, because of the need to ensure appropriate storage conditions for pharmaceutical preparations containing phenothiazines. The appearance of radical species is the only aspect of the photochemical oxidation which will be dealt with here; it was reported by several workers<sup>158, 190-192</sup> for chlorpromazine.

A second reason for the interest in light-induced formation of radicals within the phenothiazine class comes from the clinical observation that patients treated with high doses of phenothiazine drugs often show skin reactions. Lagercrantz<sup>193</sup> showed that UV irradiation of promazine solutions yielded radicals, the concentration of which, as followed by E.S.R., rapidly reached a maximum, then decayed to zero in about 1 minute, although irradiation was continued. The presence of atmospheric oxygen seems to be necessary for the formation of radicals, since thoroughly degassed solutions show no ESR signal on irradiation. Chlorpromazine displayed the same behavior in general, but the maximum was reached more slowly, and the radical was more stable. Relatively rapid decay of the latter in the dark was noted. After the disappearance of ESR signals on UV irradiation of chlorpromazine samples, the solutions turn yellow, and radical formation may now be induced by blue light, inactive toward the initial substance. The fact that these "second-generation" radicals are markedly more stable than those first formed (as shown by the shape of the concentration-time curve) is unfavorable to the hypothesis of Lagercrantz that the yellow compound acts as a sensitizer with respect to chlorpromazine, thus rendering the blue light active—the more so as the disappearance of the ESR signal on continuation of the irradiation is very naturally interpreted as a consequence of the consumption of the initial substance.<sup>194</sup> Data demonstrating that photopolymerization and other chemical processes

<sup>190</sup> L. J. Ravin, L. Kennon, and J. W. Swintosky, *J. Am. Pharm. Assoc.* **47**, 760 (1958).

<sup>191</sup> E. Pungor and E. Bruzer, *Ann. Univ. Sci. Budapest. Rolando Eotvos Nominatae, Sect. Chim.* **2**, 85 (1960); *Chem. Abstr.* **56**, 1447c (1962).

<sup>192</sup> Ch. Li Huang, *Psychopharmacol. Serv. Center Bull.* **2**, 54 (1962).

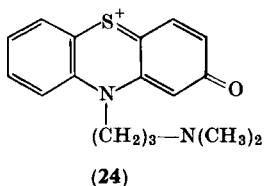
<sup>193</sup> C. Lagercrantz, *Psychopharmacol. Serv. Center Bull.* **2**, 53 (1962).

<sup>194</sup> M. S. Blois, Jr., *J. Invest. Dermatol.* **44**, 475 (1965).

occur on irradiation of chlorpromazine solutions support the view that the radicals formed on blue light irradiation are different in nature from those obtained directly from chlorpromazine.

Similar results were obtained by Blois<sup>194</sup> using visible light instead of UV. The incorporation of chlorpromazine in a growing melanin polymer points out that pigmentation of the light-exposed area observed in patients treated with chlorpromazine may be related to free-radical formation from the drug, the radicals acting, eventually, as polymerization initiators—although the activity of such highly conjugated aromatic radicals as initiators is expected to be very low.

The appearance of an intense absorption in the long-wavelength region after irradiation was proposed by Ippen<sup>195</sup> as an *in vitro* preliminary test to predict possible photoallergic side effects of new phenothiazine drugs; structure **24** is tentatively put forward by the same author for the photodecomposition product of chlorpromazine responsible for the allergic reactions.<sup>196</sup>



Enzymatic oxidation of chlorpromazine by peroxidase-H<sub>2</sub>O<sub>2</sub><sup>197,198</sup> and catalase-H<sub>2</sub>O<sub>2</sub> systems<sup>197</sup> has been reported. The red color which forms intermediately is due to the free radical; the great stability of the latter causes further enzymatic oxidation to the phenazathionium cation to play an important part in the decay of the radical, along with dismutation.<sup>198</sup>

*In vivo* formation of radical species as metabolic products of phenothiazine drugs has also been claimed (see Section VIII).

<sup>195</sup> H. Ippen, *Proc. 12th Intern. Congr. Dermatol., Washington, D.C., 1962*, Vol. 1, p. 1073. Excerpta Med. Found., 1963.

<sup>196</sup> H. Ippen, *Proc. 3rd Intern. Congr. Photobiol., Copenhagen, 1960* p. 509. Elsevier, Amsterdam, 1961.

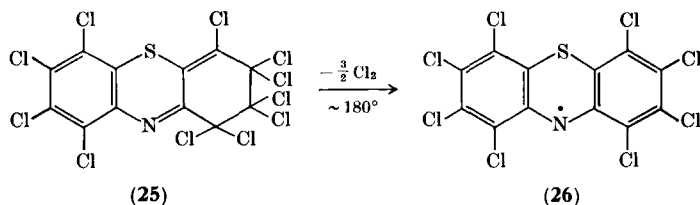
<sup>197</sup> D. J. Cavanaugh, *Science* **125**, 1040 (1957).

<sup>198</sup> L. H. Piette, G. Bulow, and I. Yamazaky, *Biochim. Biophys. Acta* **88**, 120 (1964).

## E. FORMATION OF PHENOTHIAZINYL RADICALS THROUGH HOMOLYTIC CLEAVAGES

The light-induced reaction of phenothiazine with eosin<sup>199</sup> yielded unstable free radicals which gave ESR signals with three principal lines, probably due to a bivalent nitrogen  $-\dot{\text{N}}-$ . This evidence for homolytic abstraction of a hydrogen atom from the  $-\text{NH}-$  group is supported by the fact that no ESR signal was obtained thus with *N*-substituted phenothiazines (cf. however Section IV, D). Irradiation of phenothiazine in ethanol<sup>127</sup> yielded a free radical also showing a triplet in the ESR spectrum and believed to be the neutral species S.

On thermal decomposition of 1,1,2,2,3,3,4,6,7,8,9-undecachloro-1,2-dihydro-3*H*-phenothiazine (**25**) the free radical octachlorophenothiazinyl (**26**) has been obtained in the solid state by Bodea and Silberg.<sup>200, 201</sup> Thermogravimetric and elemental analysis data confirm the following reaction:



Under different conditions of thermal decomposition the concentration of the free radical remains approximately constant at about 30%, that is, one unpaired spin for three phenothiazine moieties. The IR spectrum of the thermal decomposition product shows that no  $\text{N}-\text{H}$  bond is present, and on boiling in aniline the product is quantitatively converted into octachlorophenothiazine. This is strong evidence for a mixture of 30% free radical and 70% dimer, hexadeca-chloro-10,10'-biphenothiazine.

The free radical of octachlorophenothiazine is notable for its remarkable stability; it can be heated in air to  $300-350^\circ$  without decomposition. The ESR signal in the solid state consists of a singlet of  $4.8 \pm 0.2$  G width. In the dark-blue solutions in  $\text{H}_2\text{SO}_4$  (which

<sup>199</sup> C. Lagercrantz and M. Yhland, *Acta Chim. Scand.* **16**, 508 (1962).

<sup>200</sup> C. Bodea and I. Silberg, *Nature* **198**, 883 (1963).

<sup>201</sup> C. Bodea and I. Silberg, *Rev. Roumaine Chim.* **9**, 505 (1964).



readily dissolves the radical and completely dissociates the dimer), the ESR spectrum shows a quadruplet with line intensities 1:2:2:1. The hyperfine coupling constants  $a^N \approx a_{NH}^H = 5.9 \pm 0.1$  G, values appreciably lower than those corresponding to the unsubstituted phenothiazine (*Ca.* 7 G, see Section IV,B,3), are evidence for the increased delocalization of the unpaired electron on the side rings, as a consequence of the electron-withdrawing effect of the eight atoms of chlorine. The quadruplet arises from the protonated form of the radical (which is thus an octachloro-S<sup>+</sup>); in aprotic solvents like *o*-dichlorobenzene, a triplet is recorded, as expected for the neutral form.

A third type of homolytic cleavage leading to phenothiazinyl radicals is represented by the dissociation of 10,10'-biphenothiazines, which may be considered as tetraarylhiazines. Although 10,10'-biphenothiazines were prepared long ago by oxidation with bivalent mercury,<sup>202, 203</sup> and more recently on treating phenothiazine with phosphoric acid chlorides,<sup>204</sup> their dissociation has not been investigated, except for the hexadecachloro derivative above.

#### F. RADICALS AND CATIONS DERIVED FROM 3*H*-PHENOTHIAZINE

It was mentioned in Section I,B that 3*H*-phenothiazines are known only as derivatives in which both hydrogen atoms from position 3 are substituted. This class includes substances important as dyestuffs, which in some cases display useful biological activity.

The radicals and cations obtained from 3*H*-phenothiazines represent higher oxidation steps as compared with the corresponding species derived from phenothiazine. In fact, the completely reduced forms of the redox systems in which 3*H*-phenothiazines are involved have the same oxidation level as the completely oxidized forms of the systems in which phenothiazine participates (see Section IV,A).

Recent work on the stepwise reduction of phenothiazine dyes brought direct evidence for the existence of the intermediate semi-quinone stage, first considered by Michaelis in his work on the

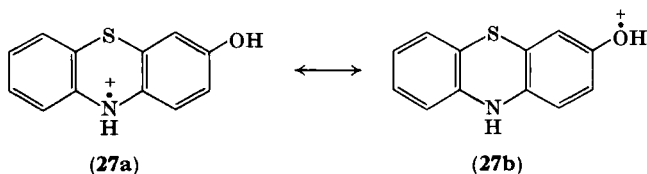
<sup>202</sup> L. Pesci, *Gazz. Chim. Ital.* **46I**, 103 (1916); *Chem. Zentr.* **I**, 936 (1916).

<sup>203</sup> C. Finzi, *Giorn. Chim. Ind. Appl.* **9**, 176 (1927); *Chem. Zentr.* **II**, 933 (1927).

<sup>204</sup> B. A. Arbuzov and D. Kh. Yarmukhametova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 1405 (1962); *Chem. Abstr.* **58**, 2468f (1963).

potentiometric titration of phenothiazine derivatives with quinonoid structures.

Electrochemical reduction of phenothiazone by Billon<sup>114, 140, 147</sup> gave quantitatively the free radical 3-hydroxy-S<sup>+</sup> (the semiquinone) which forms purple-violet solutions in 10<sup>-1</sup> *N* perchloric acid. In a neutral medium (acetonitrile) the reduction fails, probably because the stoichiometry of the reduction requires two protons. In perchloric acid two quite distinct reduction steps are recorded, at 0.13 and 0.51 V vs NCE; the ease with which the reduced forms are reoxidized significantly affects the shapes of the curves. The radical character of 3-hydroxy-S<sup>+</sup> species is confirmed by the well-resolved ESR spectra, in which four principal lines with relative intensities 1 : 2 : 2 : 1 may be distinguished—evidence for the interaction of the unpaired electron with the nitrogen nucleus and a proton. The latter may be either the proton attached to nitrogen or that of the hydroxyl group, as shown by formulations **27a** and **27b**.



Billon *et al.*<sup>140</sup> reported satisfactory agreement between observed and calculated ESR spectra, assigning the value 2.20 G for the coupling constant  $a_{\text{OH}}^{\text{H}}$ . Nevertheless, it appears more probable that the proton under discussion is the one from the NH group, since the hydroxyl proton has been shown to have no influence upon the ESR spectrum of other hydroxylated radicals,<sup>205</sup> and also the ESR spectrum of 3-methoxy-S<sup>+</sup> is very similar to that of 3-hydroxy-S<sup>+</sup> (cf. Piette *et al.*<sup>96</sup> and Billon *et al.*<sup>140</sup>).

Polarographic reduction of some phenothiazine dyes and their chemical reduction by phenylhydrazine has been reported by Schwabe and Berg.<sup>206</sup>

<sup>205</sup> J. F. Gibson, D. J. E. Ingram, M. C. R. Symons, and M. G. Townsend, *Trans. Faraday Soc.* **53**, 914 (1957).

<sup>206</sup> K. Schwabe and H. Berg, *Z. Physik. Chem. (Leipzig)* **204**, 78 (1955).

The behavior of phenothiazone with acids was investigated by Pummerer *et al.*<sup>207</sup>: hydrochloric solutions of phenothiazone, brown at first, become violet on standing. The violet compound was correctly formulated by Michaelis *et al.*<sup>208</sup> as 3-hydroxy-S<sup>+</sup>. Collier *et al.*<sup>209</sup> found that heating or standing phenothiazone in strongly acidic solutions other than hydrochloric acid, forms semiquinone. The problem was elucidated by Shine and Mach,<sup>127</sup> who showed that phenothiazone is *O*-protonated in 59% H<sub>2</sub>SO<sub>4</sub>, to form 3-hydroxy-T<sup>+</sup>. This species is unstable under these conditions and is converted into 3-hydroxy-S<sup>+</sup> by a reaction involving water, in a way similar to that leading from phenothiazine-5-oxide to S<sup>+</sup> (Scheme 2, Section IV, B, 2).

The optical spectrum of 3-hydroxy-T<sup>+</sup>, showing maxima at 287 and 444 mμ, was also recorded and interpreted by Billon,<sup>147</sup> working with acetonitrile solutions acidified with perchloric acid. The low water content of this medium probably accounts for the failure to observe semiquinone formation (no ESR signal was given by these solutions). In 96% sulfuric acid there is also no semiquinone; the 3-hydroxy-TH<sup>2+</sup> species present in these solutions may be kept unchanged for several months.

The conclusion is that there is easy interconversion of *p*- and *o*-quinonoid forms and that the sulfur atom is directly involved in all these transformations (see Scheme 3).

A particular case of interaction between acids and phenothiazones is represented by the reaction with the halogen acids. Bodea and co-workers<sup>210-213</sup> showed that addition of the acid to the quinone-imine ring of phenothiazones takes place, a behavior similar to that reported by Adams<sup>214</sup> in his papers on quinoneimines of the benzene and naphthalene series.

<sup>207</sup> R. Pummerer, F. Eckert, and S. Gassner, *Ber. Deut. Chem. Ges.* **47**, 1494 (1914).

<sup>208</sup> S. Granick, L. Michaelis, and M. P. Schubert, *J. Am. Chem. Soc.*, 1802 (1940).

<sup>209</sup> H. B. Collier, D. E. Allen, and W. E. Swales, *Can. J. Res.* **D21**, 151 (1943).

<sup>210</sup> C. Bodea and M. Răileanu, *Ann. Chem.* **620**, 88 (1959).

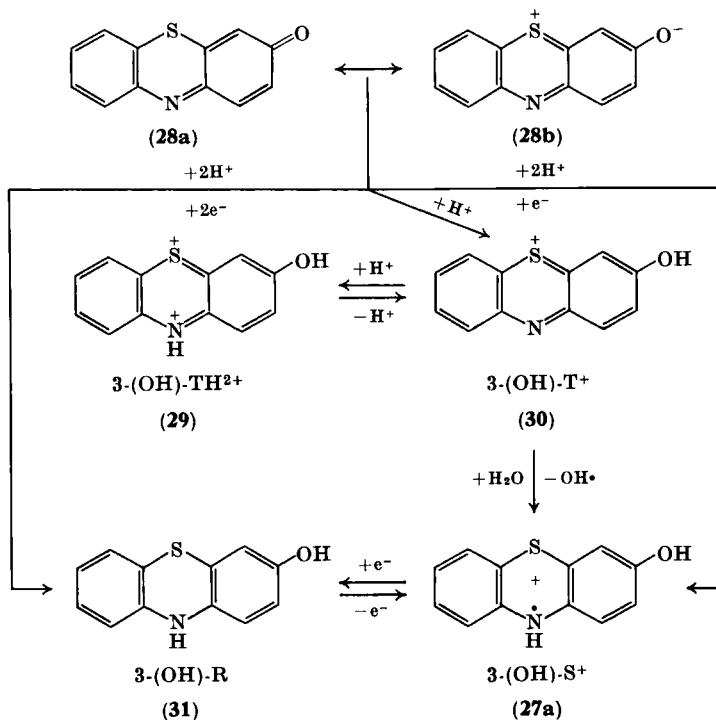
<sup>211</sup> C. Bodea and M. Răileanu, *Ann. Chem.* **631**, 194 (1960).

<sup>212</sup> C. Bodea, M. Răileanu, and I. Silberg, *Analele Stiint. Univ. "A.I. Cuza," Iasi, Sect. I* [N.S.] **6**, 1023 (1960); *Chem. Abstr.* **59**, 11478d (1963).

<sup>213</sup> C. Bodea and I. Silberg, *Rev. Chim., Acad. Rep. Populaire Roumaine* **7**, 683 (1962); *Chem. Abstr.* **61**, 8161 (1964).

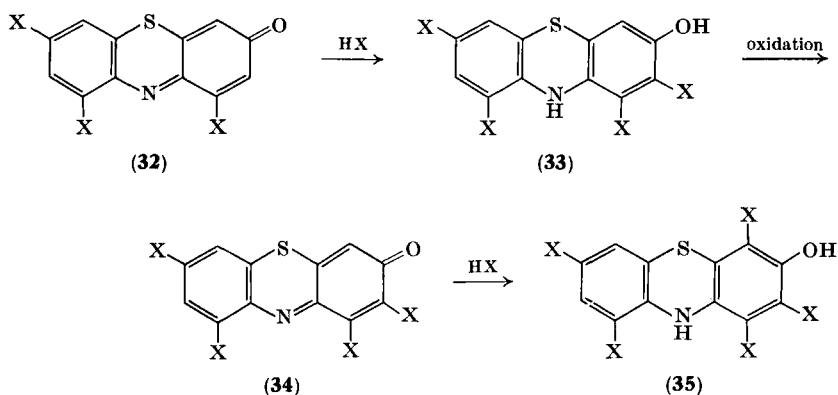
<sup>214</sup> R. Adams and W. Reifschneider, *Bull. Soc. Chim. France*, 23 (1958).

Insofar as the electronic balance is concerned, the addition of a hydrogen halide molecule is equivalent to a two-electron reduction, the reaction product being a 3-hydroxyphenothiazine. Phenothiazone



SCHEME 3

itself and some of the lower substituted halogenophenothiazones do not give any addition, owing to the great stability of the violet semi-quinone intermediate.<sup>212</sup> More highly substituted phenothiazones carrying halogens or nitro groups have more positive redox potentials and show a pronounced tendency to add hydrobromic and hydrochloric acid; some phenothiazones may undergo two successive additions—a convenient route to polyhalogenophenothiazones highly substituted on the quinoneiminic ring. In all cases so far investigated position 1 was substituted with halogen; *N*-protonation initiated 1,4 additions, giving products with the new halogen atoms in the 2- and 4-positions. Protonation of oxygen, of course, does not lead to addition, since position 1 is occupied (Scheme 4).



SCHEME 4

3-Hydroxyphenothiazines are also obtained from phenothiazones on reduction with such reagents as zinc in acetic acid or phenylhydrazine.<sup>211-213, 215-218</sup> Our view is that in these reactions the semiquinone is formed as a very unstable intermediate, observable only by the violet to green colors which precede the full decolorization of the initially red solutions.

The oxidation potential of 3-hydroxyphenothiazine is lowered in the presence of  $\beta$ -dextrin<sup>219</sup>; this was interpreted as evidence for the formation of inclusion compounds, the "spatial alkalinity" of the inner hole of  $\beta$ -dextrin molecule influencing the prototropic equilibria, which influence the stability of the semiquinone. Oxidation of 3-hydroxyphenothiazine to phenothiazone is accompanied by loss of two protons and any base facilitates this process.

Heineken *et al.*<sup>220</sup> found that a series of quinoneiminoid phenothiazine dyes, like methylene blue and its analogs, give ESR signals in sulfuric acid, the four lines of which have relative intensities 1:2:2:1. In alkaline solutions the spectrum consists of a 1:1:1 triplet. In both cases high resolutions were achieved with solutions in

<sup>215</sup> S. C. J. Olivier and W. P. Combé, *Rec. Trav. Chim.* **69**, 526 (1950).

<sup>216</sup> C. Bodea and M. Răileanu, *Ann. Chem.* **614**, 171 (1958).

<sup>217</sup> C. Bodea and V. Fărcășan, *Studii Cercetari Chim. (Cluj)* **11**, 121 (1960); *Chem. Abstr.* **55**, 14468e (1961).

<sup>218</sup> C. Bodea and M. Răileanu, *Studii Cercetari Chim. (Cluj)* **11**, 325 (1960); *Chem. Abstr.* **58**, 3420b (1963).

<sup>219</sup> W. Broser and C. Bahr, *Z. Naturforsch.* **10b**, 121 (1955).

<sup>220</sup> F. W. Heineken, M. Bruin, and F. Bruin, *J. Chem. Phys.* **37**, 1479 (1962).

stoppered phials and shaken up to total consumption of oxygen by the excess of radical. The generation of radical species in alkaline media is a noteworthy phenomenon which was also reported independently by Dallas Tuck and Schieser.<sup>125</sup> The principal coupling constants are 6.6 G in the acid solutions and 7.4 G in the alkaline. From aqueous alkaline solutions of methylene blue, the radical precipitates and may be stored for a long time in air; it has been proposed as an ESR standard. The relatively reduced influence of the substituents in the side rings on the ESR spectra is noted in this case too.

Radical species from phenothiazine dyes were also obtained on X-ray and visible light irradiation of the solutions in 23*N* H<sub>2</sub>SO<sub>4</sub><sup>221-223</sup> and it was demonstrated by ESR<sup>223</sup> and optical absorption spectra<sup>221, 222</sup> that the species thus formed are identical to those prepared by means of chemical agents (TiCl<sub>3</sub>).

Lagercrantz and Yhland<sup>224</sup> reported that from solid samples of phenothiazine dyes ESR signals may be recorded and they discussed the origin of the odd electron. The latter may appear as a consequence of  $\pi$ -delocalization extended over a great number of molecules, or may be due to semiquinone molecules trapped into the crystalline lattice.

At very low pH thionol semiquinone, that is, 3,7-dihydroxy-S<sup>+</sup> may be prepared.<sup>149</sup> This is the free radical with the highest oxidation state so far encountered within the phenothiazine class.

By the sodium mirror technique, Bruin *et al.*<sup>225</sup> obtained in dioxan anion radicals from 3,7-diaminophenothiazine (Lauth's violet), from 3,7-bis-dimethylaminophenothiazine (methylene blue), from 7-dimethylaminophenothiazone (methylene violet), and from phenothiazine itself. From the very well resolved ESR spectra of these radicals the value  $a^N \approx 7$  G was derived.

#### G. REACTIONS INVOLVING PHENOTHIAZINYL RADICALS AND PHENAZATHONIUM CATIONS

The chemical processes discussed here are those for which the existence of either a free radical or a phenazathonium cation as an

<sup>221</sup> A. J. Swallow, *J. Chem. Soc.*, 1553 (1957).

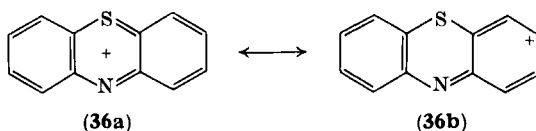
<sup>222</sup> M. Koizumi and H. Obata, *Bull. Chem. Soc. Japan* **31**, 823 (1958).

<sup>223</sup> P. B. Ayscough and C. Thomson, *J. Chem. Soc.*, 2055 (1962).

<sup>224</sup> C. Lagercrantz and M. Yhland, *Acta Chem. Scand.* **15**, 1204 (1961).

<sup>225</sup> M. Bruin, F. Bruin, and F. W. Heineken, *J. Org. Chem.* **29**, 507 (1964).

intermediate is a well-established experimental fact. Four groups of such reactions may be distinguished, viz.: (i) the so-called "oxidative coupling" (see, for example, Lewis<sup>226</sup>) of the free radicals, leading to dimers; (ii) hydrolysis of the phenazathionium cations leading to 5-oxides; (iii) hydrolysis yielding derivatives carrying oxygenated groups in position 3; (iv) nucleophilic substitutions with unoxxygenated agents. As expected for reactions proceeding through a cationic species, the last three processes are in fact reactions with nucleophilic



reagents. Furthermore, the great tendency of phenothiazine to form phenazathionium cations suggests that many substitution reactions, apparently electrophilic in nature, could be interpreted as nucleophilic substitutions. For example, there are two mechanisms that may operate when chlorine acts on phenothiazine: electrophilic substitution, through the attack of  $\text{Cl}^+$  cations in position 3 of phenothiazine, where the electron density is a maximum; or electron transfer from phenothiazine to  $\text{Cl}^+$  yielding the anion  $\text{Cl}^-$ , followed by nucleophilic attack of  $\text{Cl}^-$  at position 3, where there is the lowest electron density in the phenazathionium cation ( $36a \leftrightarrow 36b$ ). The last interpretation for the halogenation of phenothiazine and of its simple substituted derivatives is supported by the accompanying characteristic colors. Nevertheless, other reactions, like nitration, may be considered as true electrophilic substitutions of the phenothiazine heterocycle. With more electron-withdrawing substituents the formation of the phenazathionium cation is hindered and the electrophilic mechanism undoubtedly predominates.

#### 1. Dimerization of the Phenothiazinyl Free Radicals

It was pointed out in Section IV, B, 3 that the greatest spin density in the molecule of the phenothiazinyl free radicals is located on the nitrogen, sulfur, C-3 and C-7 atoms. Since the sulfur atom of phenothiazines is involved in a sulfide bridge, and has, consequently, no tendency to form a third covalence, there are only three kinds of

<sup>226</sup> J. R. Lewis, *Chem. & Ind. (London)*, 159 (1962).

bonds which might be formed from the S species. These are: (i) N—N bonds, leading to 10,10'-biphenothiazines; (ii) N—C bonds, giving 3,10'-biphenothiazines; and (iii) C—C bonds, producing 3,3'-biphenothiazines.

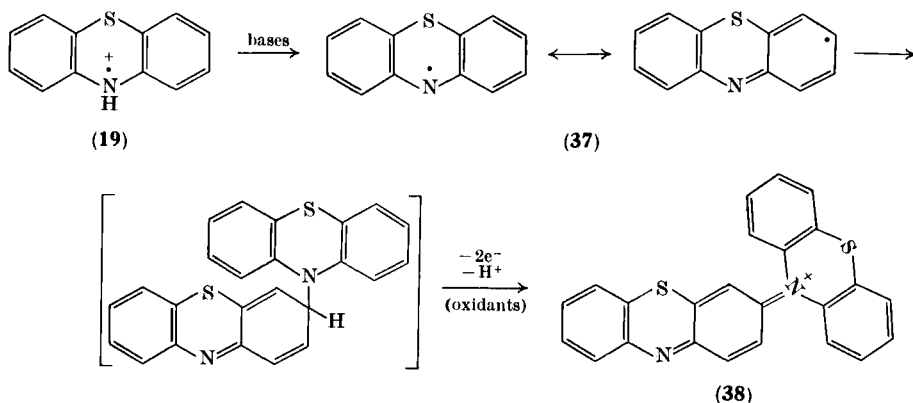
*a. Formation of N—N Bonds.* This problem was dealt with in Section IV, E. This dimerization reaction through N—N coupling is the only one which is expected to be easily reversible, by analogy with tetraarylhydrazines.

*b. Formation of N—C Bonds.* This possibility has been considered only very recently, by Foster and Hanson,<sup>130</sup> in connection with the structure of the intermediate "green product" observed by several authors in the process of the conversion of phenazathionium cations into phenothiazones. This green product is very unstable under alkaline conditions, when it is rapidly transformed into phenothiazone, but it has an appreciably longer lifetime in acid media. Billon<sup>114</sup> assigned to it the same oxidation degree as that of  $T^+$  species. The product, characterized by its absorption spectrum ( $\lambda_{\max}$  450 and 625  $m\mu$ ), was obtained either on treating  $T^+$  with water, or by carrying out the two-electron oxidation of phenothiazine in the presence of water (when two separate one-electron oxidation steps are not observed), or, finally, on treating  $S^+$  with water, when there is also a dismutation, as indicated by the formation of phenothiazine along with the green product. The same compound was observed by Cavanaugh<sup>227</sup> during the enzymatic oxidation of phenothiazine with hydroperoxides in the presence of peroxidase. He found that conversion of the green product into phenothiazone does not require oxygen; in this case the oxidation degree of the intermediate would be the same as for phenothiazone. Olivier and Combé<sup>215</sup> reported that the yield of green product on oxidation of phenothiazine with  $FeCl_3$  is markedly increased by an excess of ethanol. None of the authors succeeded in isolating this product, so that its structure is still unknown. The green product may be identical with the intermediate **40** postulated by Cymerman-Craig and Tate<sup>149</sup> and Shine and Mach<sup>127</sup> in the reactions leading from  $T^+$  to phenothiazone. Foster and Hanson,<sup>130</sup> however, considered that the conjugated system of **40** is not sufficiently extensive to account for the absorption at 630  $m\mu$ . They cited the comparison with phenothiazone (**28a**), a compound which they regarded as very similar to **40** so far as the extension of

<sup>227</sup> D. J. Cavanaugh, *J. Am. Chem. Soc.* **81**, 2507 (1959).



the conjugated system is concerned, and which presents absorption only at 505 m $\mu$ . Furthermore, water appears not to be essential for the formation of the green product. Structure **38** was proposed by Foster and Hanson for the green product; this hypothesis not only accounts for the properties so far discussed, but also explains the contradictions in the literature: **38** has the same oxidation degree as T<sup>+</sup> (as stated by Billon) and may be converted into phenothiazones,



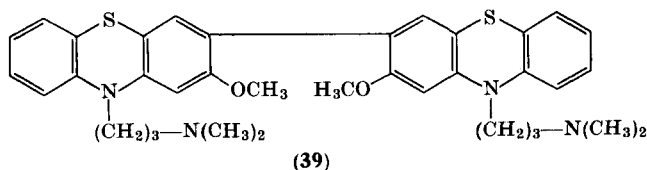
by hydrolysis without further oxidation (as claimed by Cavanaugh). The extension of the conjugated system is compatible with the low-energy absorption. It is of importance that, as shown by Musso,<sup>228, 229</sup> compounds with similar structure and properties (as regards the color and behavior on hydrolysis) were obtained in the phenoxazine series. The intense green color formed on treating phenothiazine with benzoyl peroxide<sup>230</sup> in nonpolar solvents like CCl<sub>4</sub> might also involve the formation of **38**. Insofar as the classical conditions of the preparation of the green product are concerned, water appears to play the part of a base which converts S<sup>+</sup> into S; the fact that S<sup>+</sup> is a stronger acid than H<sub>3</sub>O<sup>+</sup> results from the work of Billon<sup>147</sup> and Gilbert *et al.*<sup>119</sup>

<sup>228</sup> H. Musso, *Chem. Ber.* **92**, 2862 (1959).

<sup>229</sup> H. Musso, *Chem. Ber.* **92**, 2873 (1959).

<sup>230</sup> C. Bodea and co-workers, unpublished.

*c. Formation of C—C Bonds.* Fujisawa and co-workers<sup>231, 232</sup> claimed the formation of 3,3'-biphenothiazines, exemplified here by bimethopromazine (39), on white fluorescent light irradiation of aqueous acid solutions of some drugs in the presence of air.



There are also several reports of formation of dimers upon oxidation of various phenothiazine derivatives, without more detailed structural investigations.<sup>159, 233, 234</sup>

## 2. Hydrolysis to 5-Oxides

The *o*-quinonoid formulation of the phenazathionium cation brings out the low electron density at the sulfur atom, thus accounting for the great tendency to sulfoxide formation on treatment of cationic species with water.

*a. Formation of 5-Oxides from Electrochemically Generated Phenazathionium Cations.* Billon<sup>114, 147</sup> reported that, on electrochemical two-electron oxidation of phenothiazine and of its derivatives up to  $T^+$  species (see Section IV, B, 1), followed by treatment with hydroxylated bases, phenothiazine-5-oxides are readily obtained. A particularly pronounced tendency to yield 5-oxides is observed in the case of *N*-substituted phenothiazines; for the reasons presented in Section IV, D, the very reactive *N*-substituted dication is hydrolyzed even by traces of water. Very significant modifications of the shape of the voltametric curves are observed when oxidation is carried out at higher potentials as compared with those corresponding to  $S^+$  species, as a consequence of 5-oxide formation; the latter may sometimes be prepared in almost quantitative yield.<sup>153a, 154</sup>

<sup>231</sup> R. Yamamoto and S. Fujisawa, *Kongr. Pharm. Wiss., Vortr. Originalmitt.* **23**, 509 (1963); *Chem. Abstr.* **62**, 7750c (1965).

<sup>232</sup> S. Fujisawa and S. Kawabata, *Yakugaku Zasshi* **86**, 514 (1966); *Chem. Abstr.* **65**, 10585f (1966).

<sup>233</sup> E. Pungor, *Pharm. Acta Helv.* **35**, 173 (1960).

<sup>234</sup> E. G. Jung, M. Schwarz-Speck, and G. Kormany, *Schweiz. Med. Wochschr.* **93**, 249 (1963).

*b. Formation of 5-Oxides on Hydrolysis of Chemically Generated Cations.* The usual chemical preparative routes to phenothiazine-5-oxides are discussed in Section VII,A; only those reactions are reviewed here for which the intermediate formation of a cationic species was demonstrated. This occurs for some *N*-substituted phenothiazines of the chlorpromazine type, the oxidants being bromine,<sup>235</sup>  $\text{Mn}^{2+}$  under aerobic conditions,<sup>159, 187, 188</sup> lead tetraacetate,<sup>182</sup> and sulfuric acid.<sup>58</sup> At least two equivalents of oxidizing agent were added to the phenothiazine in each of these cases and the color due to the intermediate oxidation products was noted, thus indicating that sulfoxide formation proceeds via the phenazathionium cations.

On treatment with water of radical species derived from unsubstituted and *N*-substituted phenothiazines, especially in alkaline medium, a mixture of 5-oxide and of the initial phenothiazine derivative is obtained,<sup>114, 157</sup> as a consequence of the disproportionation of  $\text{S}^+$  species into R and  $\text{T}^+$ , followed by hydrolysis of the cation thus formed.

Enzymatic *in vitro* oxidation of chlorpromazine to chlorpromazine sulfoxide via the free radical and the phenazathionium cation has been reported.<sup>197, 198</sup>

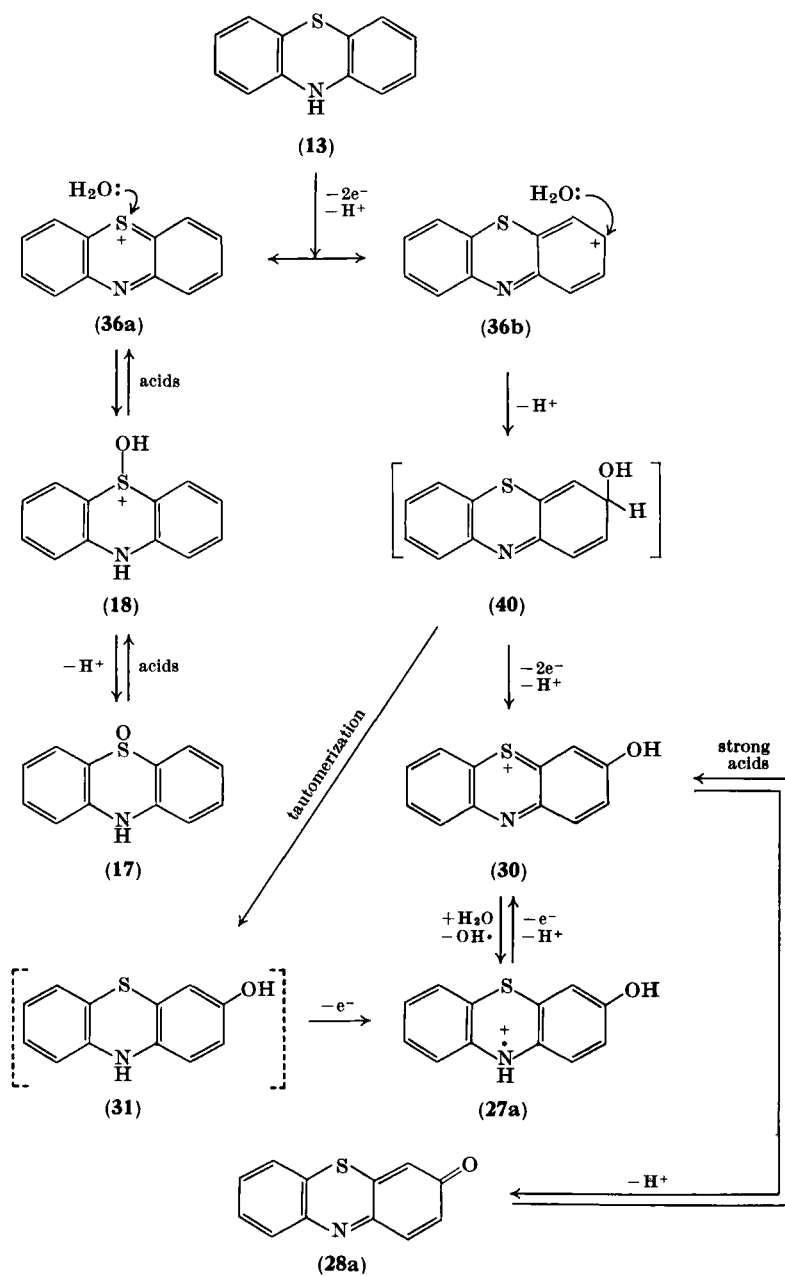
The cation corresponding to the two-electron oxidation may be generated, as mentioned in Section IV,B,2 from the 5-oxides with acids; the formation of 5-oxides from the cations is thus an "acid-reversible" reaction.

### 3. *Hydrolysis Leading to Derivatives Carrying Oxygenated Groups in Position 3*

It has long been known that oxidation of phenothiazine and its *C*-substituted derivatives in aqueous acid yields the red 3*H*-phenothiazin-3-ones (phenothiazones).<sup>2</sup> This reaction proceeds by a nucleophilic attack of water on the intermediate phenazathionium cations. The pathway of Scheme 5, after Shine and Mach,<sup>127</sup> describes the route in detail.

Nucleophilic attack of water, with loss of a proton, yields the intermediate **40**. The existence of this compound was not directly proved, but the supposition that such an intermediate does occur is a natural one. Now it may be assumed that compound **40** is oxidized (loss of two electrons and of a proton) to 3-hydroxy- $\text{T}^+$  (**30**). In the

<sup>235</sup> C. McMartin and H. V. Street, *Acta Pharmacol. Toxicol.* **21**, 172 (1964).



SCHEME 5

case of oxidations performed for preparative purposes, the oxidant required for this step is of course added in sufficient amounts; the oxidizing agent when this reaction proceeds in 59% sulfuric acid alone was suggested by Shine and Mach<sup>127</sup> to be peroxides formed from the  $\cdot\text{OH}$ -type radicals appearing in the reductive transformation of cationic species into radicals (see Scheme 2, Section IV, B, 2). 3-Hydroxy- $\text{T}^+$  is a strong acid and its conversion into phenothiazone in acetic acid proceeds rapidly. Either before it is oxidized to 3-hydroxy- $\text{T}^+$ , or parallel to this process, compound **40** may tautomerize to 3-hydroxyphenothiazine (**31**), but the formation of the latter in this reaction has not been directly observed. 3-Hydroxyphenothiazine would then be oxidized to phenothiazone, via 3-hydroxy- $\text{S}^+$  (**27a**) and, very probably, 3-hydroxy- $\text{T}^+$  (**30**). This stepwise oxidation might account for the appearance of a mixture of 3-hydroxy- $\text{T}^+$  and 3-hydroxy- $\text{S}^+$  as the final product of the transformations undergone by  $\text{T}^+$  in 59% sulfuric acid, if tautomerization were the predominant process; if not, the semiquinone (**27a**) would be formed by a process involving the homolytic cleavage of an  $\text{S}-\text{OH}$  bond, as described in Section IV, B, 2. This is very probably the case when phenothiazone is treated with 59% sulfuric acid, which yields the same mixture of hydroxylated  $\text{S}^+$  and  $\text{T}^+$  species as above.

The reaction yielding phenothiazone is obviously concurrent with that leading to 5-oxide. The acidity of the medium is the factor controlling the relative importance of these two reactions, the formation of phenothiazone requiring a strongly acidic medium. This is because, as shown above in Scheme 2 (Section IV, B, 2), the formation of 5-oxides, unlike phenothiazone formation, is an "acid-reversible" reaction; the strong acids shift the equilibrium  $5\text{-oxide} \rightleftharpoons \text{phenothiazone}$  in favor of the latter, which is slowly, but irreversibly, converted into phenothiazone. Thus, phenothiazine-5-oxides are not direct intermediates in the oxidations leading to phenothiazones,<sup>210, 211, 213, 216-218, 236, 237</sup> but appear as side products. Increase in the amount of water favors 5-oxide formation, by lowering the acidity.

Another factor influencing phenothiazone formation is the position and nature of substituents. Such substituents as methyl groups, which are difficult to replace by nucleophilic substitution, prevent

<sup>236</sup> C. Bodea and M. Răileanu, *Zh. Obshch. Khim.* **30**, 1131 (1960); *Chem. Abstr.* **55**, 550b (1961).

<sup>237</sup> C. Bodea, M. Terdic, and I. Silberg, *Ann. Chem.* **673**, 113 (1964).

phenothiazone formation, when located at both the 3 and 7 positions.<sup>147</sup> Nitro groups also hinder the reaction,<sup>210</sup> their electron-withdrawing properties rendering the formation of phenazathionium cations energetically unfavorable.

As mentioned in Section IV,C, Tozer and Dallas Tuck<sup>129</sup> investigated the correlation between rate constants of  $S^+$  decay and the nature and position of the substituents. Using a technique which eliminated the influence of all acid-reversible reactions, the rate of hydroxylation at position 3 was determined. The controlling electronic factor is the influence of the nitrogen atom at position 10, there being linear correlation between reaction rates and  $\sigma_p$  constants of the substituents at position 3 and  $\sigma_m$  constants of those located at position 2.

Another instance of transformation of the phenazathionium cation with hydroxylation in position 3 is encountered in the reaction of phenothiazine-5-oxide with 59%  $H_2SO_4$ . Shine and Mach<sup>127</sup> found that a mixture of radical species  $S^+$  and 3-hydroxy- $S^+$  is formed by dismutation and hydrolysis.

As regards the oxidants used for the preparation of phenothiazones from phenothiazines,  $FeCl_3$  gives the best yields of unsubstituted phenothiazone, when working under conditions<sup>218</sup> improved over earlier ones.<sup>215</sup> 2-Substituted phenothiazines have been recently converted into phenothiazones using  $FeCl_3$  in ethanol.<sup>238, 239</sup> Thionol has also been prepared using this reagent<sup>240</sup>; sulfuric acid was claimed to give thionol in 15% yield.<sup>241</sup> Oxidation of phenothiazine with potassium nitrosodisulfonate yielded 26.5% phenothiazone.<sup>242</sup>

Bodea *et al.* showed the utility of potassium dichromate in boiling glacial acetic acid for the preparation of halophenothiazones (e.g., 41) from halophenothiazines.<sup>210, 211, 213, 216, 217, 236, 237</sup> This reaction, proceeding via the phenazathionium cation, results in removal of a halogen atom from the position para to the nitrogen on the ring which

<sup>238</sup> S. Fujisawa and S. Kawabata, *Yakugaku Zasshi* **86**, 504 (1966); *Chem. Abstr.* **65**, 10585a (1966).

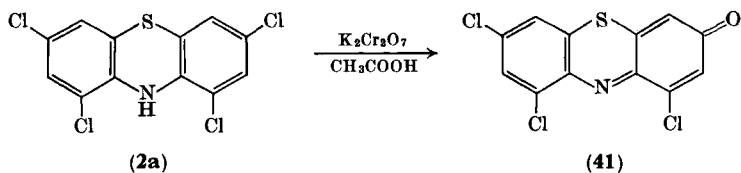
<sup>239</sup> S. Fujisawa and M. Kawamura, *Yakugaku Zasshi* **86**, 541 (1966); *Chem. Abstr.* **65**, 15373e (1966).

<sup>240</sup> P. Cardier and J. Dupontreue, *Congr. Sci. Farm. 21st Conf. Commun., Pisa, 1961*, p. 347. *Federazione Ordini Farm. Ital., Rome, 1962.*

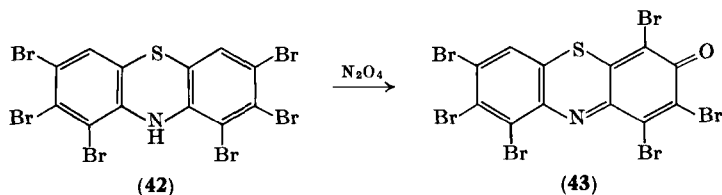
<sup>241</sup> D. F. Houston (United States of America as represented by the Secretary of Agriculture), U.S. Patent 2,516,120; *Chem. Abstr.* **45**, 673e (1951).

<sup>242</sup> L. Horner and K. Sturm, *Chem. Ber.* **88**, 329 (1955).

finally adopts the *p*-quinonoid structure. The process may be accompanied by side reactions, especially on prolonged action of dichromate, involving introduction of one or more extra halogen atoms into the phenothiazone, either by addition to the quinoneimine ring of the hydracid formed in the main reaction or by halogenation by the halogen formed on oxidation of the hydracid by dichromate. The tendency toward side reactions is particularly pronounced with



bromo derivatives. Highly halogenated phenothiazones may be obtained on oxidation of the corresponding phenothiazines with concentrated  $\text{HNO}_3$  in boiling acetic acid, or on exhaustive bromination of some nitrohalophenothiazines, when there is substitution of



nitro groups by bromine and oxidation of the bromo derivative by the nitrogen oxides so formed.<sup>243</sup> This is supported by the conversion of hexabromophenothiazine (42) into hexabromophenothiazone (43) on bubbling nitrogen oxides in a suspension of 42 in nitrobenzene; the bromine in position 4 of 43 appears as discussed above (by addition or substitution).

#### 4. Reactions of the Phenazathionium Cation with Unoxygenated Agents: The "Reductive Halogenation"

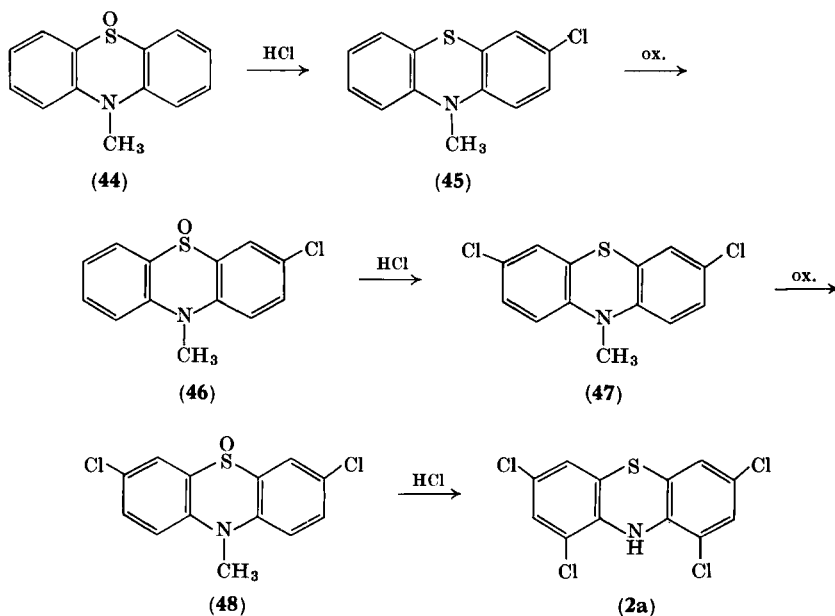
The well-known substitutions which follow the successive treatment of phenothiazine with oxidants and ammonia or amines<sup>244</sup> are

<sup>243</sup> C. Bodea and M. Terdic, *Ann. Chem.* **698**, 186 (1966).

<sup>244</sup> V. Meyer and P. Jacobsen, "Lehrbuch der Organischen Chemie," Vol. II, Part 3, p. 1490. Veit, Leipzig, 1920.

nowadays interpreted as nucleophilic attacks on the phenazathionium cation. These reactions are useful in preparing phenothiazine dyes, but, since the latter are beyond the scope of this chapter, substitutions with nitrogen-containing reagents will not be discussed here.

Another interesting reaction, for which a similar mechanism was invoked, is the action of halogenacids on phenothiazine-5-oxides, the



so-called "reductive halogenation." Early work has shown that hydrochloric acid with phenothiazine-5-oxides yields chlorophenothiazines, with removal of the sulfoxide oxygen atom (see, e.g., Page and Smiles<sup>245</sup>). Extensive work has been performed within recent years, aimed at establishing the positions occupied by the halogen atoms and clarifying the mechanism.

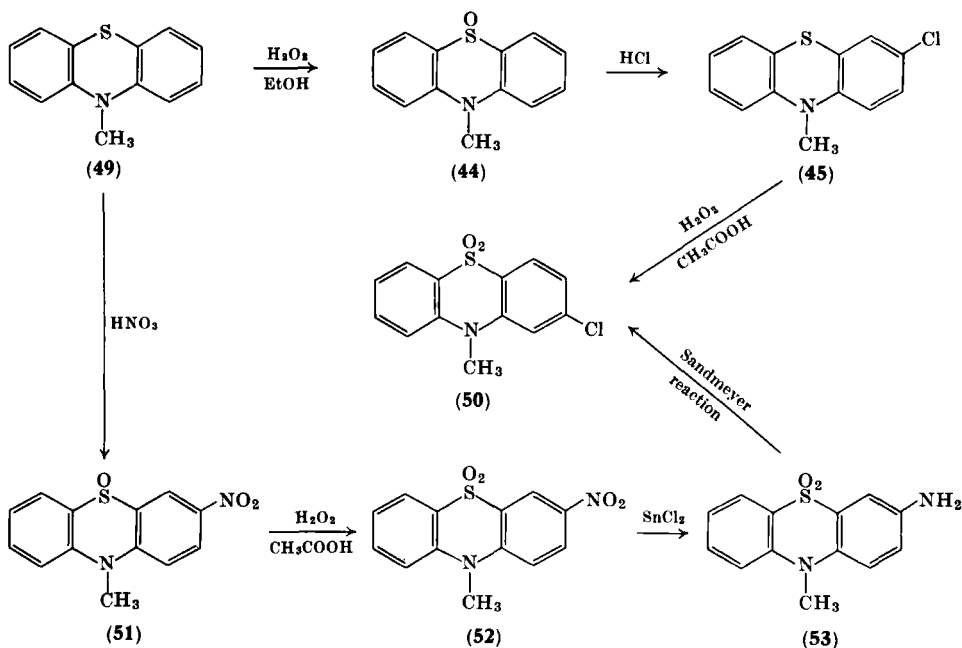
It is now established that the orientation of the reductive halogenation is controlled by nitrogen; positions 3 and 7 are occupied first, then 1 and 9. Thus Schmalz and Burger<sup>246</sup> obtained 3-chloro-10-methylphenothiazine (45) from 10-methylphenothiazine-5-oxide (44) and hydrochloric acid, and 3,7-dichloro-10-methylphenothiazine (47)

<sup>245</sup> H. J. Page and S. Smiles, *J. Chem. Soc.* **97**, 1115 (1910).

<sup>246</sup> A. C. Schmalz and A. Burger, *J. Am. Chem. Soc.* **76**, 5455 (1954).



similarly from 3-chloro-10-methylphenothiazine-5-oxide (46). Now, if 3,7-dichloro-10-methylphenothiazine-5-oxide (48) is treated with hydrochloric acid, the methyl group is removed and the product of the reaction is 1,3,7,9-tetrachlorophenothiazine (2a). 10-Ethylpheno-



SCHEME 6

thiazine behaves similarly.<sup>247</sup> The preparative interest of this reaction is illustrated by the synthesis of 1,3,7-trichlorophenothiazine, which cannot be obtained by direct chlorination of phenothiazine, but which is prepared in 54% yield when 3,7-dichlorophenothiazine-5-oxide, the unmethylated analog of 48, is treated with hydrochloric acid.<sup>248</sup>

Schmalz and Burger<sup>246</sup> tried to prove the structure of 45 by methylation of 3-chlorophenothiazine. Doubts were then expressed as to whether the substance methylated by them actually was 3-chloro-

<sup>247</sup> H. Gilman and J. Eisch, *J. Am. Chem. Soc.* **77**, 3862 (1955).

<sup>248</sup> D. Simov Antonov, *Bull. Inst. Chim., Acad. Bulgare Sci.* **2**, 75 (1953); *Chem. Abstr.* **49**, 6266e (1955).

phenothiazine<sup>249-251</sup>; the definitive demonstration was given by Simov Antonov and Karakasheva<sup>252</sup> and confirmed by Zhuravlev and Skorodumov<sup>253</sup> by the sequence of reactions presented in Scheme 6. The second atom of chlorine enters position 7.<sup>254</sup>

Reductive brominations were carried out by Gilman and co-workers<sup>99, 247</sup> on 10-ethylphenothiazine-5-oxide and 3-bromo-10-ethylphenothiazine-5-oxide, and by Bodea *et al.*<sup>255</sup> who prepared 3-nitro-7-bromo-10-methylphenothiazine from 3-nitro-10-methylphenothiazine-5-oxide.

A particular instance of reductive bromination has been reported by Bodea and Terdic.<sup>256</sup> They brominated phenothiazine-5-oxide with elementary bromine and found that bromophenothiazines are formed, containing one bromine atom more than expected on the basis of the utilized molar ratio. Thus, starting with phenothiazine-5-oxide, on treatment with 1 mole of bromine one obtains 3,7-dibromophenothiazine, with 2 moles of bromine 1,3,7-tribromophenothiazine, and with 3 moles of bromine 1,3,7,9-tetrabromophenothiazine. It was therefore assumed that the first step consists of an electrophilic substitution, leading to 3-bromophenothiazine-5-oxide (54), which immediately undergoes reductive bromination with the hydrobromic acid formed in the first reaction to give 3,7-dibromophenothiazine (55). If more bromine is used, 55 is further brominated to the tri- or tetrabromo derivative.

Attempts at reductive fluorination or iodination of phenothiazine have failed. Reduction of the 5-oxide was the only reaction which took place with either HF or HI.<sup>246, 247</sup>

<sup>249</sup> A. Mackie and A. Kutler, *J. Chem. Soc.*, 2577 (1954).

<sup>250</sup> J. Cymerman-Craig, W. P. Rogers, and G. P. Warwick, *Australian J. Chem.* **8**, 252 (1955).

<sup>251</sup> K. J. Farrington and W. K. Warburton, *Australian J. Chem.* **8**, 545 (1955).

<sup>252</sup> D. Simov Antonov and E. Karakasheva, *Bull. Inst. Chim., Acad. Bulgare Sci.* **2**, 113 (1953); *Chem. Abstr.* **49**, 5442c (1955).

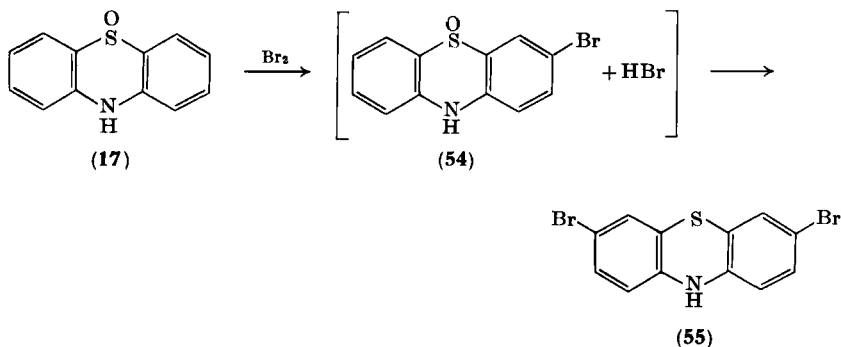
<sup>253</sup> S. V. Zhuravlev and V. A. Skorodumov, *Zh. Organ. Khim.* **1**, 202 (1965); *Chem. Abstr.* **62**, 16236a (1965).

<sup>254</sup> D. Simov Antonov, *Compt. Rend. Acad. Bulgare Sci.* **10**, 21 (1957); *Chem. Abstr.* **52**, 6357g (1958).

<sup>255</sup> C. Bodea, V. Fărcășan, and I. Oprean, *Studii Cercetari Chim. (Cluj)* **14**, 173 (1963); *Chem. Abstr.* **61**, 16067h (1964).

<sup>256</sup> C. Bodea and M. Terdic, *Studii Cercetari Chim. (Cluj)* **14**, 165 (1963); *Chem. Abstr.* **61**, 16067f (1964).

The mechanism of the reductive halogenation is still controversial. Two types of mechanism have been invoked.<sup>246, 248</sup> The first involves the formation of phenazathionium halides, followed by the nucleophilic attack of the halide ion. The second consists of an oxidation of the acid by the sulfoxide oxygen; the halogen thus formed electrophilically attacks the reduced phenothiazine.



Since strong acids very readily convert phenothiazine-5-oxides into the corresponding phenazathionium cations (see Section IV, B, 2), which show a pronounced tendency to undergo nucleophilic substitution Simov Antonov<sup>248</sup> and Schmalz and Burger<sup>246</sup> interpreted the intense colors, which always accompany the reaction and which are characteristic of the phenazathionium cation, as evidence for the nucleophilic mechanism. Experiments by Gilman and Eisch,<sup>247</sup> however, strongly support the electrophilic mechanism. Thus, if the mechanism were via the nucleophilic attack, then the yield of brominated products should be greater than that of chlorinated ones, and the best yields should be achieved in the case of reductive iodination. But in fact the reverse order is observed, more readily explained by an electrophilic mechanism. More direct evidence was obtained by the isolation of *p*-bromophenol (41% yield) when the reductive bromination was carried out in the presence of phenol.<sup>247</sup> Also, the appearance of 3,7-dichlorophenothiazine on reductive chlorination of phenothiazine-5-oxide, and of 1,3,7,9-tetrachlorophenothiazine from 3,7-dichloro-10-methylphenothiazine-5-oxide, is very difficult to explain if no cationic chlorine is involved in this process. An interesting case in this respect is that of the *N*, 5-dioxide

of 3-diethylaminopropylphenothiazine (free base)<sup>246</sup> which with HCl yields a dichlorophenothiazine (m.p. 200–202°), the side chain being lost during the reaction. At the same time it is rather hard to understand such a powerful oxidizing action as that assigned to the sulfoxide oxygen in the electrophilic mechanism—an oxidizing action that is not encountered in other reactions of the phenothiazine-5-oxides. Also against the exclusive occurrence of the electrophilic substitution in this process are the results of Shine and Dais<sup>257</sup> on the reductive halogenation of thianthrene, and the isolation by Cymerman-Craig *et al.*<sup>152</sup> of crystalline 3-chlorophenazathionium chloride, and its conversion into 3,7-dichlorophenothiazine on boiling in glacial acetic acid.

We believe that, in the reductive halogenation, the halogens almost certainly enter the phenothiazine ring via both of the mechanisms discussed above.

3,7-Dichlorophenothiazine-5-oxide<sup>248, 258</sup> and 1,3,7-trichlorophenothiazine-5,5-dioxide<sup>259</sup> were obtained on treating phenothiazine with HCl in the presence of H<sub>2</sub>O<sub>2</sub>, reactions which were interpreted as nucleophilic substitutions.

#### H. CHARGE-TRANSFER COMPLEXES OF PHENOTHIAZINES

It was mentioned in Section III,A,1 that, as indicated by the results of quantum mechanical calculations, phenothiazine is an excellent electron donor; the numerous examples in the previous subsections dealing with the oxidation of phenothiazines also illustrated the ease with which electrons are lost by the derivatives of this heterocycle. Consequently, phenothiazine charge-transfer complexes with various acceptors are expected.

The electron transferred from the highest occupied level of the donor to the lowest empty orbital of the acceptor usually spends only a small fraction of its time with the acceptor; the almost complete transfer needs energy absorption (light). It has been proposed by Karreman *et al.*<sup>35</sup> that the donor activity of phenothiazines is so

<sup>257</sup> H. J. Shine and C. F. Dais, *J. Org. Chem.* **30**, 2145 (1965).

<sup>258</sup> K. J. Farrington and W. K. Warburton, *Australian J. Chem.* **9**, 480 (1956).

<sup>259</sup> D. Simov Antonov, *Bull. Inst. Chim., Acad. Bulgare Sci.* **2**, 97 (1953); *Chem. Abstr.* **49**, 6267b (1955).

high that even in the ground state practically total transfer of an electron to the acceptor occurs when charge-transfer complexes are formed with compounds of this class. If this is so, a second absorption band in the visible, which is sometimes present in the spectrum of phenothiazine charge-transfer complexes, may be due to a reverse transition, that is, to a movement of the electron back to the donor upon light absorption.

A comparative survey<sup>130</sup> of the electron-donor abilities of some phenothiazine derivatives in the formation of charge-transfer complexes clearly illustrated the lowering of the energy of the highest occupied level, that is, the decrease of the donor tendencies, with *N*-substitution (cf. Section III, A, 2).

Foster and Fyfe<sup>260</sup> suggested that in phenothiazine drugs the reversible binding of the drug molecule at a "biological position," interaction which is essential for the pharmacological action, might involve charge-transfer-type processes.

However, because the oxidized forms of the phenothiazine derivatives are good electron acceptors, phenazathionium salts with easily polarizable anions will be expected to have more or less pronounced charge-transfer complex character, the acceptor being in this case the phenazathionium cation. Both these types of charge-transfer complexes are actually known.

#### 1. Charge-Transfer Complexes of Phenothiazine and of Its Substitution Products

Investigating the polarographic behavior of phenothiazine in the presence of oxygen, Martin *et al.*<sup>261</sup> noted the disappearance of the oxygen reduction wave and its replacement by others situated at more negative potentials. They ascribed this phenomenon to the formation of charge-transfer complexes. There is a correlation between the displacement of the polarographic wave and the oxidation potentials of the 2-substituted phenothiazines, which, in turn, may be correlated with Hammett  $\sigma_p$  constants. The authors stated that  $\sigma$  rather than  $\pi$  complexes are formed.

At low temperatures, a red equimolecular complex of phenothiazine

<sup>260</sup> R. Foster and C. A. Fyfe, *Biochim. Biophys. Acta* **112**, 490 (1966).

<sup>261</sup> H. F. Martin, S. Price, and B. J. Gudzinowicz, *Arch. Biochem. Biophys.* **103**, 196 (1963).

with sulfur dioxide was obtained; it decomposes at room temperature yielding phenothiazine as a very fine dust—a procedure to obtain highly dispersed preparations of phenothiazine.<sup>262</sup> Also relatively unstable are the complexes with  $\text{BF}_3$ .<sup>77</sup>

Very stable complexes, which may be sublimed and sometimes recrystallized, are obtained when the preparation of some phenothiazines by thionation is carried out using excess of iodine and sulfur. These complexes contain two, four, or six atoms of sulfur per phenothiazine residue, and their IR spectra are identical to those of the heterocyclic component, as expected of charge-transfer complexes.<sup>84</sup>

Complexes with high unpaired spin densities, displaying semiconductor properties, were obtained on treating phenothiazine and some of its lower halogenated derivatives with *o*- and *p*-chloranil.<sup>263</sup> Some theoretical studies concerning the ionization potentials of phenothiazines were performed using their charge-transfer complexes with quinonoid acceptors.<sup>37, 38</sup> Particularly demonstrative of the electron-donor ability of phenothiazine is the observation by Ichikawa *et al.*<sup>264</sup> of rapid hydrogen exchange at room temperature between acetylene and some quinone complexes of phenothiazine. This reaction does not proceed even at 120° in the presence of either the donor or of the acceptor only.

In a search for a mechanism of the inhibitory action exerted by chlorpromazine on some enzymatic processes, the interaction of this substance with oxidized flavines and xanthenes was investigated, and the formation of charge-transfer complexes was observed.<sup>265–268</sup> There are many indications that the phenothiazine-melanine interaction, which is probably involved in the retinotoxicity of some phenothiazine drugs, is also of the donor-acceptor type, as suggested

<sup>262</sup> J. B. J. Zaba (Imp. Chem. Ind. Ltd.) British Patent 768,454; *Chem. Abstr.* **51**, 12446c (1957).

<sup>263</sup> A. Wilson (American Cyanamid Co.) U.S. Patent 3,117,125; *Chem. Abstr.* **60**, 8040h (1964).

<sup>264</sup> M. Ichikawa, M. Soma, T. Onishi, and K. Tamaru, *J. Phys. Chem.* **70**, 3020 (1966).

<sup>265</sup> S. Kistner, *Acta Chem. Scand.* **14**, 1389 (1960).

<sup>266</sup> K. Yagi, T. Ozawa, and T. Nagatsu, *Biochim. Biophys. Acta* **43**, 310 (1960).

<sup>267</sup> E. Lábos, *Nature* **209**, 201 (1966).

<sup>268</sup> J. E. Maruchin, *Farm. Polska* **22**, 177 (1966); *Chem. Abstr.* **65**, 10424g (1966).

by Potts<sup>269-273</sup> (cf., however, Blois<sup>194</sup>). Interesting from the biological viewpoint are also the complexes of phenothiazines with polyphosphates (including nucleic acids)<sup>274</sup> and with some metals<sup>275</sup>; the latter have also been dealt with in other connections.<sup>135, 276</sup>

Complexes between phenothiazines and cobalt thiocyanate<sup>277</sup> and with some ingredients in the pharmaceutical preparations<sup>278</sup> were also reported.

## 2. Charge-Transfer Complexes of Phenazathionium Cations

In earlier literature there are reports of the formation of perhalides on treatment of phenothiazine with bromine and iodine<sup>279-281</sup>; these are now considered to be charge-transfer complexes. The phenothiazine component normally acts as a donor and the electronegative halogens as acceptors, but here total transfer of electrons occurs and the phenothiazine is oxidized. Phenothiazine and 3,7-dimethylphenothiazine behave similarly in the presence of strong organic acceptors, like dicyanobenzoquinone and dichlorodicyanobenzoquinone.<sup>130</sup>

On the other hand, the highly halogenated hexabromo- and octabromophenothiazine with excess of bromine yield unstable dark-blue charge-transfer complexes, as noted by Rupprecht.<sup>153</sup> The highly electronegative substitution entails a marked increase of the redox potential, so that total transfer of the electron from the phenothiazine to the free bromine does not occur. On thermal decomposition, these complexes yield the unchanged bromophenothiazine; in the IR spectra of the complexes there is, as expected, an N—H stretching band<sup>230</sup> (cf. following paragraphs).

<sup>269</sup> A. M. Potts, *Invest. Ophthalmol.* **1**, 522 (1962).

<sup>270</sup> A. M. Potts, *Invest. Ophthalmol.* **3**, 399 (1964).

<sup>271</sup> A. M. Potts, *Invest. Ophthalmol.* **3**, 405 (1964).

<sup>272</sup> A. M. Potts, *Arch. Ophthalmol.* **72**, 359 (1964).

<sup>273</sup> A. M. Potts, *Trans. Am. Ophthalmol. Soc.* **60**, 517 (1962).

<sup>274</sup> P. Hele, *Biochim. Biophys. Acta* **76**, 647 (1963).

<sup>275</sup> G. C. Cotzias and D. C. Borg, *Res. Publ., Assoc. Res. Nervous Mental Disease* **40**, 337 (1960).

<sup>276</sup> M. S. Usova and N. F. Gaeva, *Anal. Abstr.* **5**, 114 (1958).

<sup>277</sup> P. Mesnard and J. Lagubeau, *Compt. Rend.* **260**, 3993 (1965).

<sup>278</sup> J. L. Lach and M. Bornstein, *J. Pharm. Sci.* **54**, 1730 (1965).

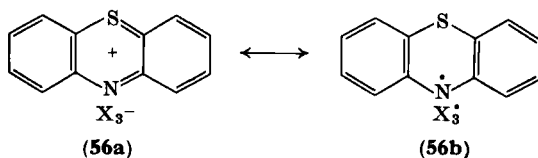
<sup>279</sup> F. Kehrman and O. Vessely, *Ann. Chem.* **322**, 34 (1902).

<sup>280</sup> R. Pummerer and S. Gassner, *Ber. Deut. Chem. Ges.* **46**, 2321 (1913).

<sup>281</sup> F. Kehrman and L. Dieserens, *Ber. Deut. Chem. Ges.* **48**, 318 (1915).

When oxidation does take place, the phenazathionium cation so formed acts as an acceptor with respect to the polarizable perhalide ion—as occurs also with pyridinium and pyrylium salts (cf. Balaban *et al.*<sup>282</sup>). More recent data concerning iodine complexes<sup>132, 283–285</sup> show that these substances are semiconductors with high conductivity and marked paramagnetism, and that there are three atoms of iodine per phenothiazine residue. The IR spectra are similar to those of the phenazathionium bromide.

The presence of unpaired spins in the phenazathionium per iodides is not evidence for the semiquinonoid character of the phenothiazine component, but shows that the charge-transfer toward the cation is very important, the limiting structure (**56b**) being closer to the real state of the molecule.



This is especially well marked in the octahalophenazathionium perhalides obtained by Bodea and Silberg<sup>286</sup> on exhaustive chlorination of bromophenothiazines or on treating undecachlorodihydrophenothiazine with bromine. These perhalides without hydrogen atoms in the molecule should not form semiquinone salts  $S^+$ , because this would require an NH group in the molecule, which would be easily detectable in the IR spectra. As a consequence of their pronounced tendency to adopt a **56b**-type structure, the thermal decomposition of these octahalophenazathionium perhalides starts at relatively low temperatures (about 40–50°) yielding gaseous products consisting either of bromine or of a mixture of bromine and chlorine—and the free radicals, which remain as such, in the same  $\approx 30\%$  concentration which was encountered in the thermal decomposition of undecachlorodihydrophenothiazine (see Section IV,E).

<sup>282</sup> A. T. Balaban, M. Mocanu, and Z. Simon, *Tetrahedron* **20**, 119 (1964).

<sup>283</sup> A. E. Szent-Györgyi, J. Isenberg, and S. L. Baird, Jr., *Proc. Natl. Acad. Sci. U.S.* **46**, 1444 (1960).

<sup>284</sup> Y. Matsunaga, *Helv. Phys. Acta* **36**, 800 (1963).

<sup>285</sup> F. Gutmann and H. Keyzer, *Electrochim. Acta* **11**, 1163 (1966).

<sup>286</sup> C. Bodea and I. Silberg, *Rev. Roumaine Chim.* (1968) (in press).



## V. Ring Substitution Reactions of Phenothiazines

Phenothiazine substitution reactions have been much studied in recent years. This work was stimulated by the search for new phenothiazine derivatives with useful pharmacological properties and by the commercial availability of unsubstituted phenothiazine.

### A. C-SUBSTITUTION

#### 1. Halogenation

Although the reaction of chlorine and bromine with phenothiazine has been long investigated, reproducible methods leading to well-defined halogenated derivatives were described only within the last 15 years. Even for products like 1,3,7,9-tetrachlorophenothiazine which were characterized in the earlier literature, the definitive demonstration of the positions occupied by the chlorine atoms was performed only recently, and the methods of preparation have been substantially improved.

Chlorinated, brominated, and iodinated derivatives have been prepared by halogenation of phenothiazine. Direct fluorination is unknown. All fluorinated phenothiazines (see, for example, Roe and Little<sup>88</sup>) have been made by ring closure. Thiocyanation of phenothiazine has also been reported.

Along with the elementary halogens, other reagents, such as  $S_2Cl_2$ ,  $S_2Br_2$ ,  $SOCl_2$ ,  $SO_2Cl_2$ ,  $PCl_5$ , and  $PBr_5$ , have been used for halogenating phenothiazines. The special case of "reductive halogenation," i.e., the preparation of halogenated phenothiazines by the action of halogen acids on phenothiazine-5-oxides, was discussed in Section IV, G, 4.

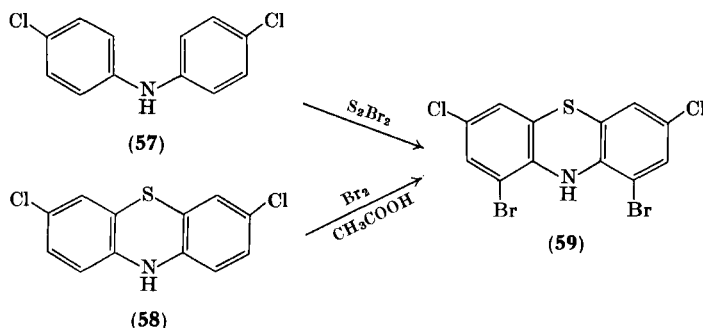
*a. Chlorination with Elementary Chlorine.* By the action of chlorine upon phenothiazine under various conditions, well-defined chlorinated derivatives have been prepared, containing from two up to eleven chlorine atoms in the molecule.

On treating phenothiazine with a calculated amount of chlorine in glacial acetic acid Bodea and Răileanu<sup>287</sup> obtained a mixture of chlorinated products consisting mainly of di- and tetrachlorophenothiazine, from which 3,7-dichlorophenothiazine was isolated in 33% yield by extraction with acetone at room temperature. The procedure

<sup>287</sup> C. Bodea and M. Răileanu, *Studii Cercetari Chim. (Cluj)* **9**, 159 (1958); *Chem. Abstr.* **55**, 15497b (1961).

for obtaining 3,7-dichlorophenothiazine by means of  $\text{PCl}_5$ , described below (Section V,A,1,d), is to be preferred from the preparative point of view.

The structure of 3,7-dichlorophenothiazine was demonstrated in several ways. Rupprecht<sup>153</sup> obtained 1,9-dibromo-3,7-dichlorophenothiazine (59) from the reaction of 4,4'-dichlorodiphenylamine (57) with  $\text{S}_2\text{Br}_2$  (following Zerweck<sup>288</sup>) and this mixed halogenated compound was identical with the product of the bromination of 3,7-dichlorophenothiazine (58) with bromine in acetic acid.



By the Sandmeyer reaction, Simov Antonov<sup>289</sup> converted 3,7-diaminophenothiazine-5,5-dioxide (60) into 3,7-dichlorophenothiazine-5,5-dioxide (61) which proved to be identical with the 5,5-dioxide obtained by the oxidation of 3,7-dichlorophenothiazine (58). There is also some less direct evidence supporting this structure.

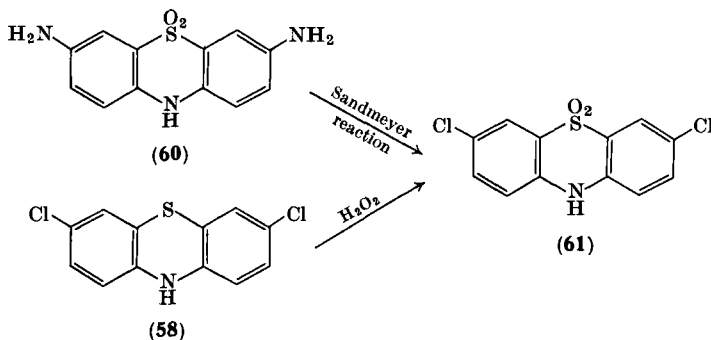
No trichlorophenothiazine could be isolated on direct chlorination; however, chlorine with phenothiazine in nitrobenzene is the best method of preparing 1,3,7,9-tetrachlorophenothiazine (80% yield).<sup>210</sup> The structure of the tetrachloro derivative was demonstrated by desulfurization by Raney nickel to 2,4,2',4'-tetrachlorodiphenylamine (7).<sup>290</sup>

<sup>288</sup> W. Zerweck, BIOS/TIDU Reel FDX 863 Frame 1703 (unpublished photocopy) quoted by Rupprecht.<sup>153</sup>

<sup>289</sup> D. Simov Antonov, *Compt. Rend. Acad. Bulgare Sci.* **9**, 57 (1956); *Chem. Abstr.* **51**, 17927e (1957).

<sup>290</sup> D. Simov and A. Petrova, *Compt. Rend. Acad. Bulgare Sci.* **10**, 293 (1957); *Chem. Abstr.* **54**, 6728a (1960).

Rupprecht<sup>153</sup> described the preparation of some highly chlorinated derivatives by the catalyzed chlorination of phenothiazine. In the absence of UV irradiation, he claimed the preparation of a hexachloro derivative. The present authors have failed to reproduce this result; no authentic report of the preparation of pure hexachlorophenothiazine is to be found in the literature to date. On UV irradiation, chlorination leads to 1,2,3,4,6,7,8,9-octachlorophenothiazine, which was isolated laboriously in small yield. This substance is readily



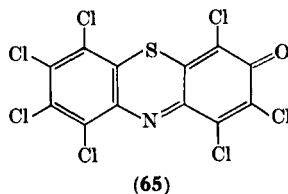
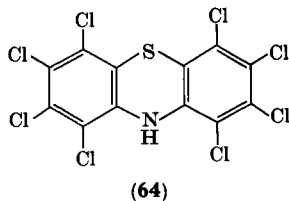
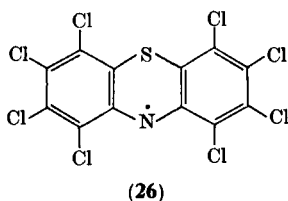
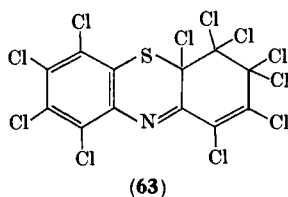
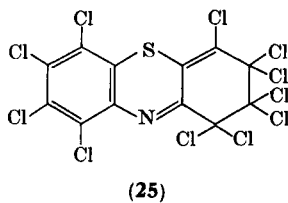
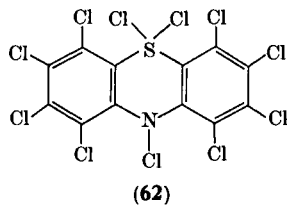
available in 50% yield, if the suspension of tetrachlorophenothiazine formed on chlorination of phenothiazine in nitrobenzene is further treated with chlorine.<sup>237</sup>

Bodea and Silberg<sup>291</sup> showed that nitrobenzene is an excellent reaction medium for the preparation of highly chlorinated phenothiazines; not only are the usual substitution reactions leading to tetra- and octa-chlorophenothiazine best performed in this solvent, but on prolonged action of chlorine an "exhaustive chlorination" involving also addition of chlorine takes place, yielding an "undecachlorophenothiazine."\* Using labeled chlorine (Cl<sup>36</sup>) evidence has been obtained that all of the chlorine atoms are attached to carbon, thus excluding structure 62; undecachlorophenothiazine has therefore either structure 25 or 63 and is to be considered as a derivative of 1,2-, or 4,4a-dihydro-3H-phenothiazine.

<sup>291</sup> C. Bodea and I. Silberg, *Rev. Roumaine Chim.* **9**, 425 (1964).

\* Name used for brevity and convenience; 25 and 63 are more properly called undecachlorodihydrophenothiazines (editors).

Undecachlorophenothiazine has properties very different from the other halogenated phenothiazines. Particularly remarkable are its solubility in organic solvents and its high reactivity. It shows a great tendency to regain the aromaticity of its highly halogenated ring, as in the thermal decomposition when three atoms of chlorine are



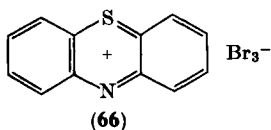
lost with formation of the stable free radical octachlorophenothiazinyl (26) (see Section IV, E), in the reduction with phenylhydrazine which yields octachlorophenothiazine (64), and in the reaction with acetic anhydride leading to heptachloro-3*H*-phenothiazin-3-one (65).

The chlorination of phenothiazine-5-oxide, proceeds similarly to that of phenothiazine; the sulfoxide oxygen is lost and 1,3,7,9-tetrachlorophenothiazine (**2a**) is formed.<sup>237</sup>

The action of chlorine on phenothiazine-5,5-dioxide in acetic acid<sup>287</sup> or in nitrobenzene at room temperature<sup>237</sup> yields 1,3,7-trichlorophenothiazine-5,5-dioxide. The lowering of the reactivity in electrophilic substitutions by oxidation at the sulfur bridge is also shown by the fact that 1,3,7,9-tetrachlorophenothiazine-5,5-dioxide is the final product of chlorination even in nitrobenzene at 100°.<sup>237</sup>

Direct chlorination was also used with some substituted phenothiazines. Bromophenothiazines are chlorinated in nitrobenzene to octahalophenazathionium perhalides, as mentioned in Section IV,H,2. There are also reports on the chlorination of some nitrophenothiazines. Thus, if chlorine is bubbled through the reaction mixture prepared on treating phenothiazine with nitric acid, chloronitrophenothiazine-5-oxides of unknown orientation were obtained.<sup>292</sup> When chlorination of nitrophenothiazines is carried out in nitrobenzene, chlorine replaces the nitrogroups; e.g., 3-nitro-10-methylphenothiazine was converted into octachlorophenothiazine.<sup>230</sup>

*b. Bromination with Elementary Bromine.* The formation of phenazathionium perbromide (**66**) by the action of bromine on



phenothiazine was reported in the earlier literature.<sup>279-281</sup> These perbromides are unstable and give, on standing, ring brominated derivatives. This conversion is quantitative when the perbromides are boiled in glacial acetic acid, as shown by Kupka<sup>293</sup> for 1,3,7,9-tetrabromophenothiazine and Bodea and Răileanu<sup>211</sup> for 3,7-dibromo- (**55**), 1,3,7-tribromo- (**73**), and 1,3,7,9-tetrabromophenothiazine (**69**). A monobromo derivative cannot be obtained by this procedure.

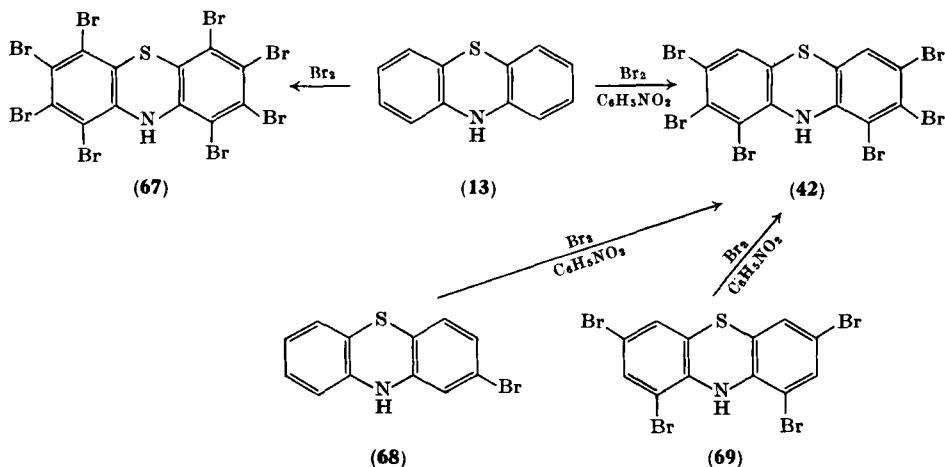
Tetrabromophenothiazine is the highest brominated derivative which may be prepared on bromination in glacial acetic acid. As in

<sup>292</sup> F. Maennchen (Farbwerke Hoechst A.-G. vorm. Meister Lucius & Brüning), German Patent 837,536; *Chem. Abstr.* **51**, 15610c (1957).

<sup>293</sup> R. Kupka, unpublished dissertation, München (1951).

the case of chlorination with chlorine, nitrobenzene is the best reaction medium for polybromination. Bodea *et al.*<sup>237</sup> prepared 1,2,3,7,8,9-hexabromophenothiazine (42) with bromine and phenothiazine or tetrabromophenothiazine (69) in nitrobenzene on a steam bath. The structure of this substance was established by the preparation of an identical hexabromo derivative from 2-bromophenothiazine (68). The action of bromine in nitrobenzene at 100° is a specific route to other hexahalo derivatives, as shown below.

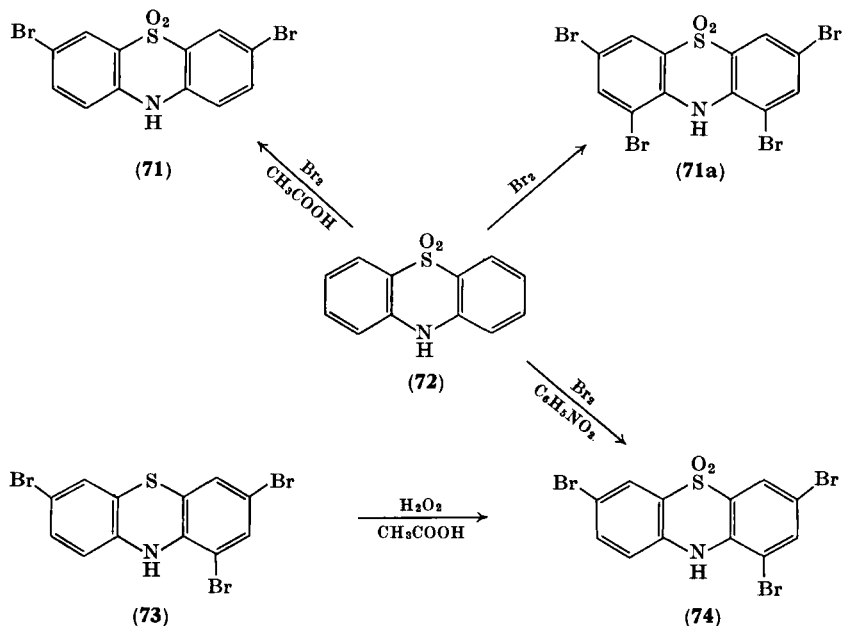
The substitution of the last two hydrogen atoms of the benzene rings, leading to octabromophenothiazine (67), requires very severe conditions, viz. refluxing phenothiazine with bromine without solvent. Rupprecht<sup>153</sup> recommended the use of iodine and of iron filings as catalysts in this reaction, but it has been shown<sup>237</sup> that they are superfluous. The immediate result of the reactions in which highly brominated phenothiazines are prepared is the formation of dark-blue charge-transfer complexes, as mentioned in Section IV, H, 2.



The bromination of phenothiazine-5-oxide probably proceeds via the phenazathionium cation and was therefore discussed in Section IV, G, 4.

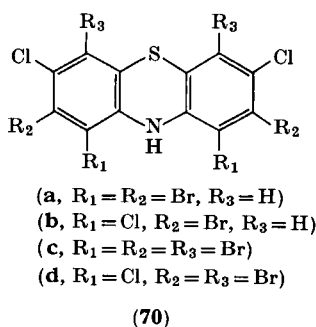
In boiling glacial acetic acid the bromination of phenothiazine-5,5-dioxide (72) yields only a 3,7-dibromo derivative (71),<sup>237</sup> unlike chlorination, where at room temperature a trichloro derivative was formed (Section V, A, 1, a). 1,3,7-Tribromophenothiazine-5,5-dioxide

(74) may be prepared by working in nitrobenzene at 150°; it is identical with the product of oxidation with  $\text{H}_2\text{O}_2$  of 1,3,7-tribromophenothiazine (73). By refluxing 72 with bromine, an almost quantitative yield of 1,3,7,9-tetrabromophenothiazine-5,5-dioxide (71a) was obtained.<sup>237</sup>



There is also a series of chlorobromophenothiazines, which may be prepared either acting with chlorine on bromophenothiazines (see Section IV, H, 2) or brominating chlorophenothiazines. The preparation of 3,7-dichloro-1,9-dibromophenothiazine (59) on bromination in glacial acetic acid was already mentioned (Section V, A, 1, a); using nitrobenzene at 100° as a solvent, Bodea and Silberg<sup>286</sup> prepared 3,7-dichloro-1,2,8,9-tetrabromo- (70a) and 1,3,7,9-tetrachloro-2,8-dibromophenothiazine (70b) from the corresponding chlorophenothiazines. The same chlorinated derivatives were converted, on boiling in bromine, into octahalo derivatives (70c and 70d), two further bromine atoms being thus introduced in positions 4 and 6.

Unlike phenothiazine, the 10-methyl derivative can be monobrominated in the 3-position.<sup>294</sup> Ring bromination in glacial acetic acid occurs here at room temperature. With 2 moles of bromine, also at room temperature, 3,7-dibromo-10-methylphenothiazine was prepared. The action of 3 moles of bromine did not lead to a tribromo derivative but to 1,3,7,9-tetrabromophenothiazine (**69**), the methyl group being removed. Steric considerations are not entirely sufficient to explain this behavior, since bromination of 3-nitro-7-chloro-10-

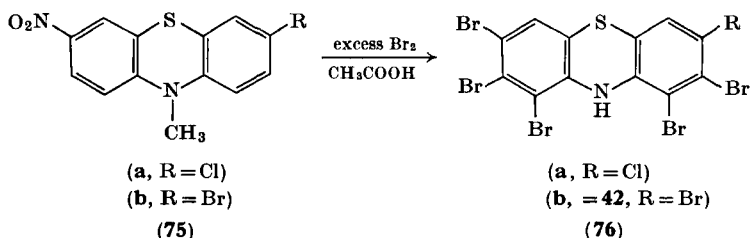


methylphenothiazine (**75a**) yielded a 9-bromo derivative (**77**) with retention of the methyl group.<sup>255</sup> This problem is rather puzzling primarily because the exact nature of the substitution mechanism is unknown here. Indeed, the fact that a monobromo derivative can be obtained from 10-methylphenothiazine might be interpreted as a consequence of the lowering of the reactivity toward electrophilic reagents by introduction of an alkyl group in position 10, for the reasons explained in Sections III,A,2 and IV,D. But then the ring substitution at room temperature is surprising, remembering that bromination of unsubstituted phenothiazine requires boiling in acetic acid; nor is the removal of the *N*-methyl group satisfactorily accounted for on the basis of electrophilic substitution. It may be supposed, however, that there is oxidation of 10-methylphenothiazine by bromine prior to substitution; the oxidation potential of 10-methylphenothiazine is higher than that of phenothiazine (Section IV,D) and this would account for the lowering of the reactivity (monosubstitution). In exchange, the 10-methylphenazathionium dication

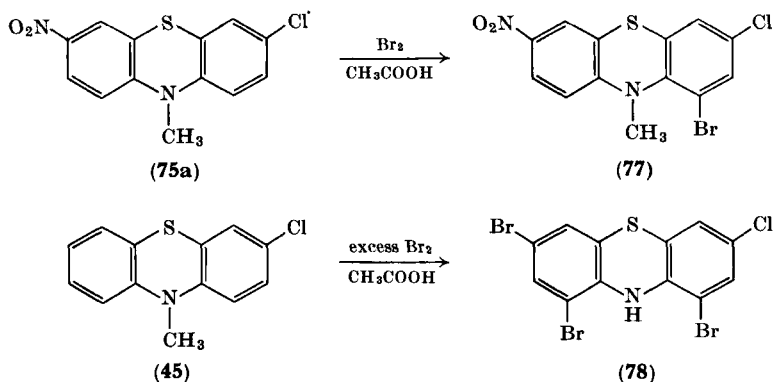
<sup>294</sup> C. Bodea and M. Terdic, *Studii Cercetari Chim. (Cluj)* **13**, 81 (1962); *Chem. Abstr.* **59**, 11477h (1963).



once formed, it is far more reactive than the  $T^+$  species derived from phenothiazine (see Section IV, G, 2, *a*), and this explains the completion of the reaction at room temperature. The *o*-quinonoid structure of 10-methyl- $T^{2+}$  species makes the removal of the methyl group appear more natural. With nitro derivatives, of course, the redox potential becomes so high that bromine cannot act as an oxidant toward the phenothiazine, and true electrophilic substitution takes place.



Bromination of **75a** in glacial acetic acid with excess of bromine not only removes the methyl group but also replaces the nitro group by bromine; 7-chloro-1,2,3,8,9-pentabromophenothiazine (**76a**) is formed. This bromination at positions 2 and 8 (usually possible only in



nitrobenzene) in acetic acid solution, in the case of the mononitrophenothiazines, occurs again in the preparation of 1,2,3,7,8,9-hexabromophenothiazine (**42**) on bromination of 3-nitro-7-bromo-10-methylphenothiazine (**75b**).<sup>255</sup> The somewhat paradoxical part played by the nitro group in this reaction is underlined by the fact that

bromination of 3-chloro-10-methylphenothiazine (**45**) under the same conditions stops at the tetrahalo-stage (**78**).<sup>255</sup>

The 5,5-dioxides of **75a** and **75b** cannot be brominated under these conditions.

*c. Iodination with Elementary Iodine.* The reaction of iodine with phenothiazine merely forms phenazathionium periodides (see Sections IV, H, 2 and V, A, 1, *b*); no ring-iodinated phenothiazine was prepared on further working up of these compounds. Gilman and Eisch<sup>247</sup> failed to iodinate 10-ethylphenothiazine with iodine under various conditions. 3-Iodo-10-ethylphenothiazine was prepared on treating 10-ethylphenothiazine-5-oxide with iodine. In this case, there is at least a formal analogy with the bromination of phenothiazine-5-oxide,<sup>256</sup> in that there is an apparent facilitation of the ring halogenation by the presence of sulfoxide oxygen (see Section IV, G, 4).

*d. Chlorination with  $S_2Cl_2$ ,  $SOCl_2$ ,  $SO_2Cl_2$ , and  $PCl_5$ .* The chlorinating action of  $S_2Cl_2$  was observed in the reactions in which this substance was used as a thionating agent for diphenylamine<sup>288</sup> and 4,4'-difluorodiphenylamine,<sup>153</sup> the product of the reaction being in both cases 1,3,7,9-tetrachlorophenothiazine (**2a**). It is of interest to note the replacement of fluorine with chlorine in the second case, an unusual phenomenon for such aromatic fluoro derivatives; on the other hand, Spasov<sup>32</sup> claims that no tetrachlorophenothiazine may be obtained on treating diphenylamine with  $S_2Cl_2$  (see Section II, C).

Chlorination accompanying thionation was also encountered with  $SOCl_2$  (Section II, A).

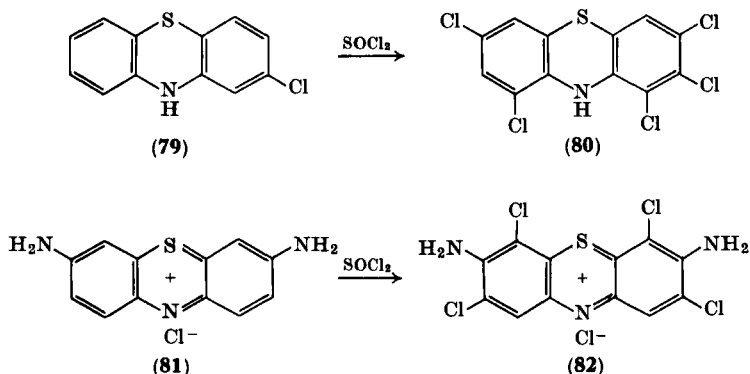
The use of  $SOCl_2$  as a chlorinating agent for phenothiazine and for some of its derivatives has been reported in several papers. Rupprecht<sup>153</sup> cites unpublished work<sup>293</sup> describing the preparation of 1,3,7,9-tetrachlorophenothiazine by the action of thionyl chloride on phenothiazine. Kanô and Fujimoto<sup>22</sup> confirmed this result, showing also that phenothiazine-5-oxide yields the same product, with loss of the sulfoxide oxygen. Phenothiazine-5,5-dioxide does not react with thionyl chloride.

When *C*-substituted phenothiazines are chlorinated by  $SOCl_2$ , the chlorine atoms enter the most reactive positions; for example, 2-chlorophenothiazine (**79**) is converted into 1,2,3,7,9-pentachlorophenothiazine (**80**),<sup>22</sup> and thionine (**81**) is claimed to give 2,4,6,8-tetrachloro-3,7-diaminophenazathionium chloride (**82**).<sup>295</sup>

<sup>295</sup> M. Fujimoto, *Bull. Chem. Soc. Japan* **32**, 480 (1959).

As with the cyclization of *N*-substituted diphenyl-amines with  $\text{SOCl}_2$  (Section II, A), the chlorination of *N*-substituted phenothiazines with thionyl chloride is accompanied by removal of the 10-substituent.<sup>295, 296</sup>

Attempts to prepare phenothiazine-1- and phenothiazine-2-carboxylic acid chlorides with  $\text{SOCl}_2$  gave acid chlorides ring-chlorinated in positions 3,7,9 and 1,3,7,9, respectively.<sup>153, 297, 298</sup> The preparation of a dichlorophenothiazine-1-carboxylic acid chloride of unknown orientation from  $\text{SOCl}_2$  and a suspension of 1-carboxyphenothiazine in benzene has recently been reported.<sup>299</sup>



There is lack in agreement over the use of sulfuryl chloride as a chlorinating agent. Fujimoto<sup>300</sup> stated that tetrachlorophenazathionium chloride is obtained from phenothiazine, phenothiazine-5-oxide, and the tetrachlorophenothiazine. However, Spasov and Panov<sup>301</sup> prepared tetrachlorophenothiazine from phenothiazine-5-oxide, and octachlorophenothiazine from tetrachlorophenothiazine. Surprisingly,

<sup>296</sup> M. Fujimoto and H. Kanô (Shionogi & Co., Ltd.), Japanese Patent 6631 (1959); *Chem. Abstr.* **54**, 15409a (1960).

<sup>297</sup> N. V. Savitskaya and M. N. Shchukina, *Zh. Obshch. Khim.* **24**, 152 (1954); *Chem. Abstr.* **49**, 3202i (1955).

<sup>298</sup> A. Burger and J. B. Clements, *J. Org. Chem.* **19**, 1113 (1954).

<sup>299</sup> J. S. Driscoll and R. H. Nealey, *J. Heterocyclic Chem.* **2**, 272 (1965).

<sup>300</sup> M. Fujimoto, *Bull. Chem. Soc. Japan* **32**, 483 (1959).

<sup>301</sup> A. Spasov and N. Panov, *Godishnik Sofiiskiya Univ., Fiz. Mat. Fak., Khim.* **54**, 233 (1961); *Chem. Abstr.* **56**, 11581h (1962).

chlorination of 10-acylphenothiazines with  $\text{SO}_2\text{Cl}_2$  also yields octachlorophenothiazine; this cannot be obtained from unsubstituted phenothiazine.<sup>301</sup>

Phosphorus pentachloride was used by Kupka<sup>293</sup> to prepare 3,7-dichlorophenothiazine from phenothiazine. This method was improved by Strell and Rupprecht<sup>302</sup> and it is now the best way of making 3,7-dichlorophenothiazine, the yield being over 90% (cf. Section V, A, 1, a).

In an attempted Beckmann rearrangement of 2-acetyl-10-methylphenothiazine oxime with  $\text{PCl}_5$  at  $50^\circ$ , Cauquil *et al.*<sup>303</sup> obtained a monochloro derivative, formed in a side reaction.

4. *Brominations with  $\text{S}_2\text{Br}_2$  and  $\text{PBr}_5$ .* The cyclization of 4,4'-dichlorodiphenylamine (57) with  $\text{S}_2\text{Br}_2$  to 1,9-dibromo-3,7-dichlorophenothiazine (59) was already mentioned in Section V, A, 1, a.<sup>153</sup> In this reaction cyclization probably takes place before bromination.

The preparation of 3,7-dibromophenothiazine using  $\text{PBr}_5$  as described for the corresponding chlorinated derivative was also reported.<sup>153, 302</sup>

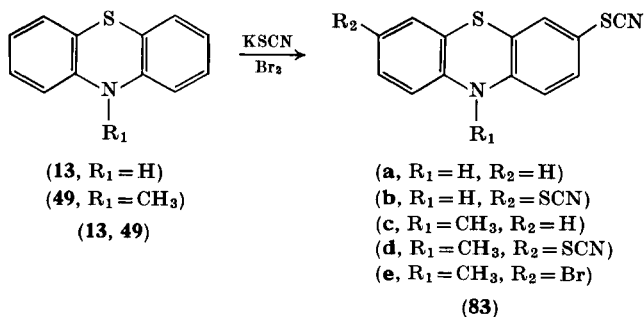
f. *Brominations with Bromate-Bromide Mixture.* With the object of identifying and estimating phenothiazine drugs and their metabolic products, bromination with  $\text{KBrO}_3$ - $\text{KBr}$  mixture was undertaken. McMartin and Street<sup>235</sup> investigated in further detail the color reaction given by phenothiazines with bromine in sulfuric acid, which had been described by Lucas and Fabierkiewicz,<sup>170</sup> who concluded from UV and IR spectra that dibromo-5-oxides are formed in a reaction with bromine generated by a bromate-bromide mixture acidified with sulfuric acid; the coloration used for analytical purposes is that given by these 5-oxides on reaction with  $\text{H}_2\text{SO}_4$ . McMartin and Street demonstrated that phenothiazine-5-oxide and a monobromophenothiazine-5-oxide are intermediates. These results do not contradict those reported in Section IV, G, 4, concerning the loss of the sulfoxide oxygen on bromination of the sulfoxides, because in the oxidizing medium provided by the presence of the bromate-bromide mixture continuous oxidation up to the phenazathionium cation and hydrolysis of the latter to the sulfoxide takes place. The

<sup>302</sup> M. Strell and M. Rupprecht, German Patent 938,669; *Chem. Abstr.* **53**, 8173a (1959).

<sup>303</sup> G. Cauquil, E. Casadevall, and A. Casadevall, *Bull. Soc. Chim. France*, 608 (1962).

oxidizing power of  $\text{KBrO}_3$ -KBr mixture seems to be enhanced on acidification with hydrochloric instead of sulfuric acid; a dibromodioxide was thus isolated in the case of chlorpromazine.<sup>304</sup>

*g. Thiocyanation.* Bodea and Terdic reported the thiocyanation of phenothiazine,<sup>305</sup> phenothiazine-5-oxide,<sup>256</sup> and 10-methylphenothiazine<sup>294</sup> under the conditions of the Kaufmann<sup>306</sup> method and with



$(\text{SCN})_2$ . In all cases no higher substituted compound than a dithiocyanato derivative was obtained. Thiocyanogen reacted with phenothiazine and phenothiazine-5-oxide, but not with 10-methylphenothiazine, again exemplifying the effect of an alkyl group in position 10. Thiocyanato derivatives of 10-methylphenothiazine (49) were obtained only by means of Kaufmann's method. It is possible that in some of these reactions phenazathionium bromides are formed, which undergo then a nucleophilic attack of the  $\text{SCN}^-$  ion. However, treating 10-methylphenothiazine with only 1 mole of alkali thiocyanate, gave 3,7-thiocyanatobromo-10-methylphenothiazine (83e).

The thiocyanation of phenothiazine-5-oxide, both with thiocyanogen and by Kaufmann's method, yielded only 3,7-dithiocyanato-phenothiazine (83b), with removal of the oxygen from sulfur.

## 2. Nitration

Recently the nitration of phenothiazine has been clarified and most of the controversy in the early literature over the structure and

<sup>304</sup> E. Szabolcs, *Acta Pharm. Hung.* **34**, 212 (1964); *Chem. Abstr.* **61**, 15936e (1964).

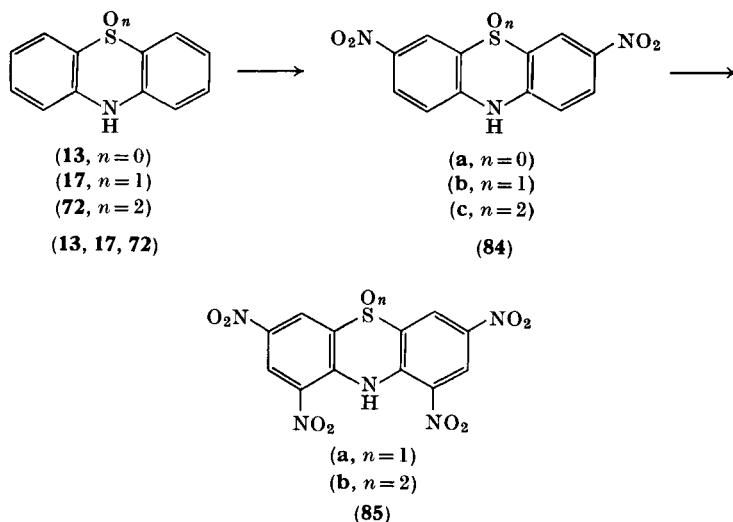
<sup>305</sup> C. Bodea and M. Terdic, *Studii Cercetari Chim. (Cluj)* **12**, 309 (1961); *Chem. Abstr.* **61**, 4341d (1964).

<sup>306</sup> H. P. Kaufmann and W. Oehring, *Ber. Deut. Chem. Ges.* **59**, 187 (1926).

purity of nitrophenothiazines has been resolved. Nitration played an important part in establishing the orientation rules of substitution in the phenothiazine ring.

Nitric acid and nitrites in acid medium have been used as nitrating agents in the preparation of nitrophenothiazines. In the case of  $\text{HNO}_3$ , nitration is always accompanied by oxidation at sulfur to 5-oxides or 5,5-dioxides, depending upon the concentration of the acid and the substituents in the ring. Using nitrites in acid medium, nitro derivatives unoxidized at sulfur are obtained.

a. *Unsubstituted Phenothiazine, Phenothiazine-5-oxide, and Phenothiazine-5,5-dioxide.* Nitration of phenothiazine with nitric acid may be used to obtain in the pure state Kehrman's 3-nitrophenothiazine-



5-oxide<sup>307</sup> and 1,3,7,9-tetranitrophenothiazine-5-oxide (**85a**).<sup>308-310</sup> 3,7-Dinitrophenothiazine-5-oxide (**84b**) is prepared pure only by oxidation of 3,7-dinitrophenothiazine (**84a**) with  $\text{HNO}_3$ <sup>310</sup> (cf., however, Driscoll and Nealey<sup>299</sup>).

<sup>307</sup> F. Kehrman and P. Zybs, *Ber. Deut. Chem. Ges.* **52**, 132 (1919).

<sup>308</sup> Ch. Monard, H. Ficherouille, and R. Fournier, *Mem. Poudres* **34**, 179 (1952).

<sup>309</sup> K. Toei, *Nippon Kagaku Zasshi* **76**, 1083 (1955); *Chem. Abstr.* **51**, 11913d (1957).

<sup>310</sup> C. Bodea and M. Răileanu, *Studii Cercetari Chim. (Cluj)* **8**, 303 (1957); *Chem. Abstr.* **54**, 22657g (1960).

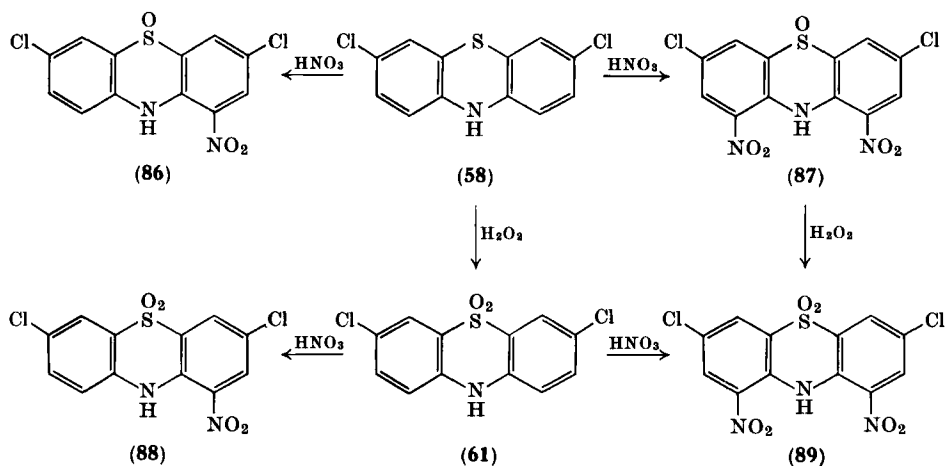
Nitration of phenothiazine-5-oxide has not been thoroughly investigated; however, using  $\text{HNO}_3$  *d.* 1.42, pure 3-nitrophenothiazine-5-oxide can be obtained in good yield.<sup>230</sup>

Depending upon the conditions, phenothiazine-5,5-dioxide (72) may be nitrated to 3-nitro-,<sup>310</sup> 3,7-dinitro- (84c),<sup>310</sup> or 1,3,7,9-tetra-nitrophenothiazine-5,5-dioxide (85b).<sup>310, 311</sup>

The above data indicate that oxidation to 5-oxide and 5,5-dioxide does not modify the order of the reactivity of the different positions, and in all these cases the heterocyclic nitrogen atom directs nitro groups into the usual 1,3,7,9-positions, although with the oxidized derivatives a decreased reactivity toward nitrating agents was noted, as for halogenation.

Pure 3,7-dinitrophenothiazine is obtained on treating phenothiazine with sodium nitrite and acetic acid in chloroform<sup>310</sup>; phenothiazine-5-oxide does not react under these conditions.

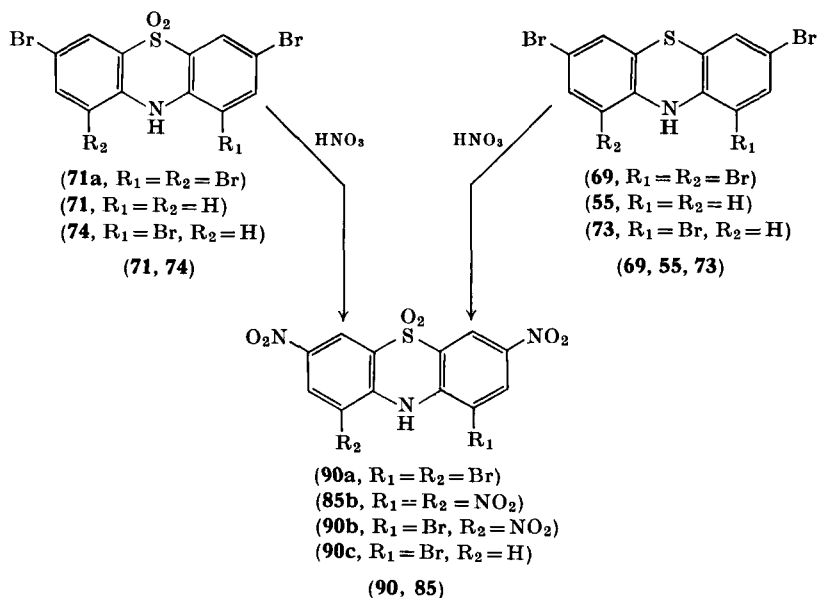
*b. C-Substituted Phenothiazines, Phenothiazine-5-oxides, and Phenothiazine-5,5-dioxides.* Bodea *et al.* investigated the action of nitric acid upon some chlorophenothiazines, chlorophenothiazine-5,5-



SCHEME 7

<sup>311</sup> K. Toei, *Nippon Kagaku Zasshi* **77**, 1270 (1956); *Chem. Abstr.* **52**, 961i (1958).

dioxides,<sup>79, 287</sup> and bromophenothiazines and bromophenothiazine-5,5-dioxides.<sup>312</sup> In the chlorophenothiazines one or two nitro groups were introduced, entering unsubstituted positions, if any, controlled by the directing effect of the heterocyclic nitrogen. Chlorophenothiazines underwent a parallel oxidation to 5-oxides and in some cases to 5,5-dioxides.<sup>79</sup> Nitration of 3,7-dichlorophenothiazine and of its 5,5-dioxide may be presented as an example (Scheme 7).



The direct action of  $\text{HNO}_3$ , *d.* 1.5, often leads to unidentified degradation products. Chloronitro derivatives having free reactive positions are nitrated under these conditions without oxidative breakdown.

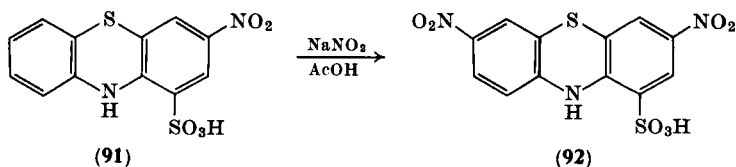
Bromophenothiazines and their 5,5-dioxides on treatment with nitric acid (*d.* 1.5) undergo replacement of the bromine from positions 3 and 7 by nitro groups.<sup>312</sup> The latter cannot replace the bromine atoms from positions 1 and 9 but can occupy these positions when free. Thus, 1,3,7,9-tetrabromophenothiazine-5,5-dioxide (71a) is converted into 1,9-dibromo-3,7-dinitrophenothiazine-5,5-dioxide

<sup>312</sup> C. Bodea, V. Fărcășan, and I. Oprean, *Zh. Obshch. Khim.* **34**, 2369 (1964); *Chem. Abstr.* **61**, 9493e (1964).



(90a) and 3,7-dibromophenothiazine-5,5-dioxide (71) yields 1,3,7,9-tetranitrophenothiazine-5,5-dioxide (85b). Under the same conditions, 1,3,7-tribromophenothiazine-5,5-dioxide (74) leads to 1-bromo-3,7,9-trinitrophenothiazine-5,5-dioxide (90b).

Starting with bromophenothiazines unoxidized at sulfur the same products as above are obtained with  $\text{HNO}_3$  (*d.* 1.5); that is, nitration is accompanied by oxidation to the 5,5-dioxide (see also Section VII,A).



Nitration of 3,7-dibromophenothiazine-5,5-dioxide (71) at positions 1 and 9 probably precedes the substitution by nitro groups of the bromine atoms from positions 3 and 7, as indicated by the isolation of the 1-nitro-3,7-dibromo-5,5-dioxide (90c) when acetic acid is used as a diluting medium.

The conversion of 3-nitrophenothiazine-1-sulfonic acid (91) into 3,7-dinitrophenothiazine-1-sulfonic acid (92) by sodium nitrite and acetic acid has recently been reported.<sup>313</sup>

Highly nitrated, explosive derivatives of methylene blue, of uncertain structure, were obtained by Urbański *et al.*<sup>314, 315</sup> (see Section VI,C,1).

*c. N-Substituted Phenothiazines, Phenothiazine-5-oxides, and Phenothiazine-5,5-dioxides.* In the *N*-substituted series, nitrated derivatives with rigorously established structure have been obtained only from 10-methyl- and 10-ethylphenothiazine. On treating 10-methylphenothiazine with  $\text{HNO}_3$  (*d.* 1.4), Skorodumov *et al.*<sup>316</sup> obtained a

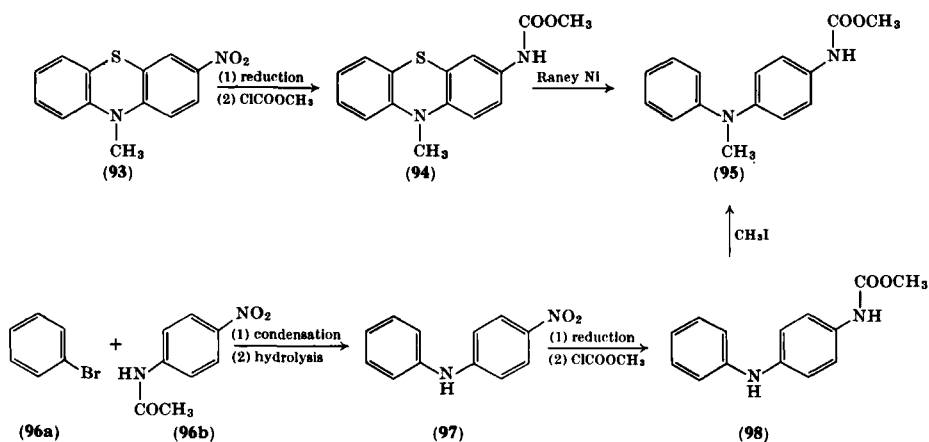
<sup>313</sup> R. Havemann, H. Pietsch, and H. Reiche, *Z. Wiss. Phot., Photophysik Photochem.* **58**, 3 (1964).

<sup>314</sup> T. Urbański, K. Szye-Lewańska, and P. Kalinowski, *Bull. Wojskowej Akad. Tech.* **7**, 56 (1957); *Chem. Abstr.* **53**, 5269i (1959).

<sup>315</sup> T. Urbański, K. Szye-Lewańska, and P. Kalinowski, *Bull. Acad. Polon. Sci., Ser. Sci. Chim., Geol. Geograph.* **7**, 147 (1959).

<sup>316</sup> V. A. Skorodumov, E. N. Il'chenko, and S. V. Zhuravlev, *Zh. Obshch. Khim.* **30**, 1680 (1960); *Chem. Abstr.* **55**, 1624d (1961).

mixture containing 3-nitro-10-methylphenothiazine and its 5-oxide, in partial contradiction with the results reported by Schmalz and Burger,<sup>246</sup> who reported only the unoxidized nitrated derivative under the same conditions. The latter authors stated that, on nitrating 10-methylphenothiazine-5-oxide, 3-nitro-10-methylphenothiazine was obtained, with loss of the sulfoxidic oxygen—surprising behavior in the presence of nitric acid—and that, to prepare the sulfoxide, 99.5%  $\text{HNO}_3$  is required. However, Bodea *et al*<sup>255</sup> confirmed the results of Skorodumov. Oxidation to the 5-oxide accompanies nitration of 10-ethylphenothiazine.<sup>246, 252, 317</sup>



SCHEME 8

Position 3 as the site of nitration of 10-methylphenothiazine was demonstrated by Zhuravlev and Skorodumov<sup>318</sup> by obtaining the same 4-substituted *N*-methyldiphenylamine (95) in two different ways (Scheme 8).

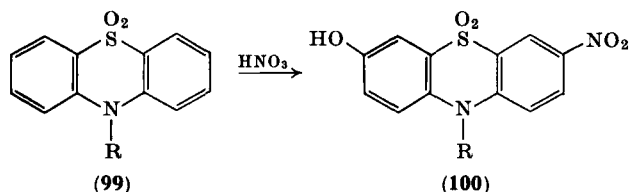
*N*-Substituted nitro derivatives, oxidized at sulfur but of unknown

<sup>317</sup> D. Simov Antonov, *Izv. Khim. Inst., Bulgar. Akad. Nauk* **5**, 51 (1957); *Chem. Abstr.* **55**, 16556d (1961).

<sup>318</sup> S. V. Zhuravlev and V. A. Skorodumov, *Zh. Organ. Khim.* **1**, 142 (1965); *Chem. Abstr.* **62**, 16236a (1965).

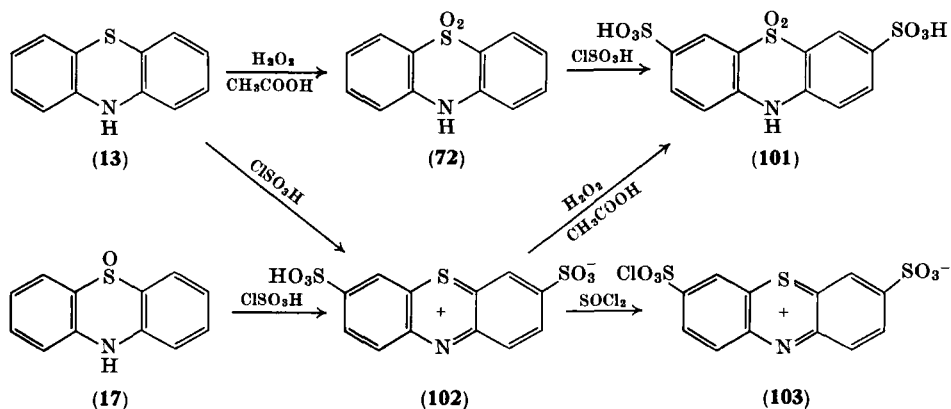
orientation, were obtained by Simov *et al.* from 10-benzylphenothiazine<sup>319</sup> and phenothiazine-10-acetic acid derivatives.<sup>320</sup> Nitrosulfides in the chlorpromazine series have also been prepared.<sup>321</sup>

An interesting "oxidative nitration" of 10-dialkylaminoalkylphenothiazine-5,5-dioxides, (99), involving the concomitant introduction of a nitrogroup (in position 3) and a hydroxyl (in position 7), (100), was reported recently by Wunderlich and Stark.<sup>322</sup>



### 3. Sulfonation

Sulfuric acid converts phenothiazine into various oxidation products (see Section IV, B, 2). Using chlorosulfonic acid, sulfonyl



SCHEME 9

<sup>319</sup> D. Simov and N. Nenov, *Godishnik Sofitskiya Univ., Fiz. Mat. Fak., Khim.* **55**, 97 (1962); *Chem. Abstr.* **59**, 6393h (1963).

<sup>320</sup> D. Simov and S. Fakirov, *Godishnik Sofitskiya Univ., Khim. Fak.* **56**, 111 (1963); *Chem. Abstr.* **61**, 9493b (1964).

<sup>321</sup> S. Masaiti and N. Hō (Yoshitomi Seyaku Kabusiki kaisia), Japanese Patent 7674 (1960).

<sup>322</sup> H. Wunderlich and A. Stark, *Pharmazie* **21**, 56 (1966).

groups were introduced into positions 3 and 7 in the molecule of phenothiazine and of its 5,5-dioxide (Scheme 9) by Fujimoto.<sup>300</sup> Phenothiazine-5-oxide gives the same product as phenothiazine.

Zwitterionic phenazathionium structures have been put forward for phenothiazine disulfonic acid (**102**) and for its acid chloride (**103**) because they are both strongly colored.

The preparation of a disulfonyl derivative of phenothiazine, also using chlorosulfonic acid, is described in a patent.<sup>323</sup>

"Oxidative sulfonation" of 10-dialkylaminoalkylphenothiazine-5, 5-dioxides, leading to the corresponding 3-hydroxy-7-sulfonic acids, has been reported<sup>322</sup> (cf. the analogous oxidative nitration, Section V, A, 2, c).

#### 4. Alkylations and Acylations

*a. Catalytic Alkylation.* Alkylation of the benzene rings of phenothiazine has recently been reported. Catalysts like  $\text{BF}_3$ , *p*-toluene sulfonic acid, etc., were successfully used for the preparation of 3,7-dialkyl derivatives on treatment with 1- and 2-alkenes.<sup>324, 325</sup>

The preparation of 1-ethylphenothiazine by reacting phenothiazine with ethylene in the presence of aluminum anilide is of special interest.<sup>326</sup> The orientation was proved by thionation of 2-ethyldiphenylamine. A mechanism involving an *N*-aluminum derivative which sterically favors the substitution in position 1 by the intermediate formation of a cyclic complex would account for this course of the reaction.

*b. Condensations with Aldehydes and Ketones.* Phenothiazine readily reacts with formaldehyde in acetic acid yielding a mixture of condensation products, the phenothiazine residues being linked by methylene bridges, probably in the positions para to the heterocyclic nitrogen, since the IR spectra clearly show the presence of NH bonds. *N*-Methylphenothiazine and phenothiazine-5-oxide do not react with formaldehyde under these conditions.<sup>230</sup>

<sup>323</sup> J. N. Duperray (Chimietechnic Union Chimique du Nord et du Rhône), French Patent 1,314,521; *Chem. Abstr.* **59**, 6418b (1963).

<sup>324</sup> J. S. Elliot, E. D. Edwards, and A. D. Brazier (Castrol Ltd.), British Patent 889,341; *Chem. Abstr.* **57**, 3448b (1962).

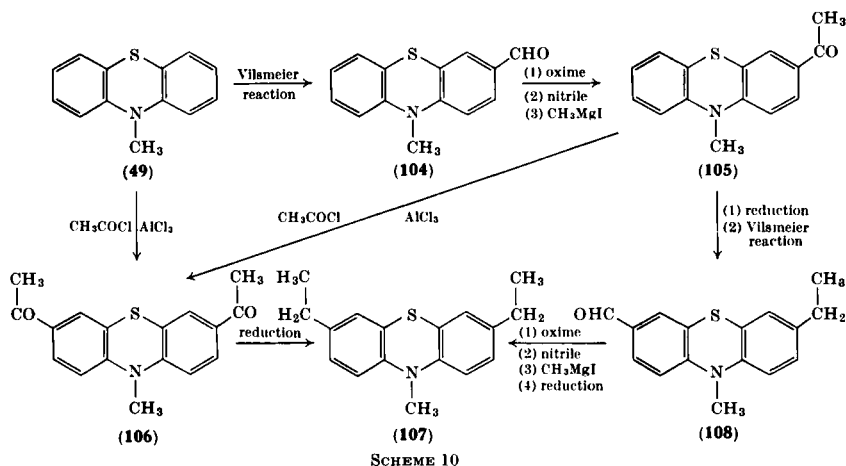
<sup>325</sup> D. R. Randell (Geigy Co. Ltd.), British Patent 1,036,696; *Chem. Abstr.* **65**, 15394h (1966).

<sup>326</sup> R. Stroh and W. Hahn, *Ann. Chem.* **623**, 176 (1959).

Wizinger and Chatterjee<sup>327</sup> condensed phenothiazine with some diaryl ketones, flavone, and coumarin, in the presence of either  $\text{POCl}_3$  or  $\text{ZnCl}_2$ , and obtained monosubstituted derivatives. These derivatives are green in acid and red in alkaline media and probably have quinonoid structures.

Michler's ketone was also condensed with 3-fluorophenothiazine.<sup>153</sup> Mixed condensation of phenothiazine and dimethylaniline with formaldehyde yielded nonresinous, oil-soluble products, useful as antioxidants.<sup>328</sup>

*c. Friedel-Crafts Acylations.* Numerous acylations of phenothiazine and *N*-alkyl- and *N*-acylphenothiazines under Friedel-Crafts conditions have been reported. Generally the acyl residues enter para to



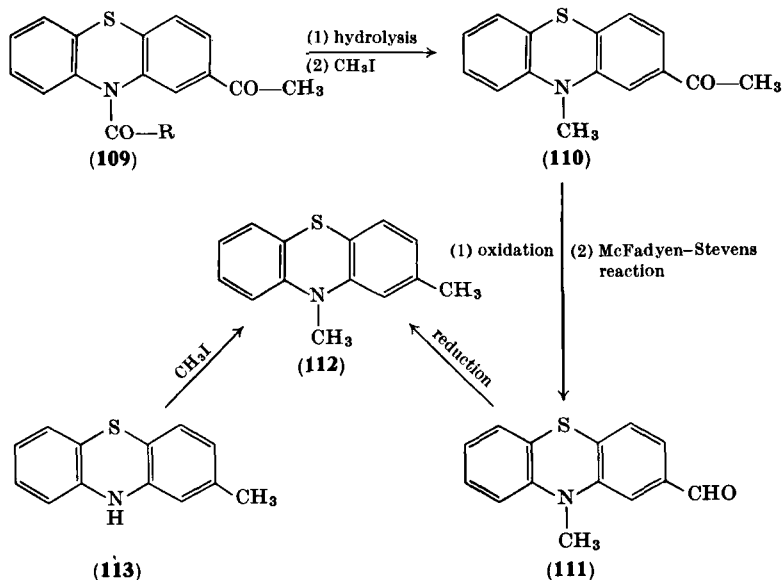
nitrogen in *N*-alkylphenothiazines and para to sulfur in *N*-acylphenothiazines. Acylation of phenothiazine itself is confused, probably because both *N*- and *C*-acylation occur.<sup>68</sup> Acetic anhydride in the presence of aluminum chloride yielded a diacetyl derivative of unknown orientation.<sup>90</sup> The orientation of the phenothiazine dicarboxylic acid obtained from phosgene and phenothiazine with fused  $\text{AlCl}_3$ ,  $\text{NaCl}$ , and  $\text{KCl}$  at  $120\text{--}140^\circ$  is also unknown.<sup>329</sup>

<sup>327</sup> R. Wizinger and S. Chatterjee, *Helv. Chim. Acta* **35**, 316 (1952).

<sup>328</sup> H. G. Smith and T. L. Cantrell (Gulf Oil Corp.), U.S. Patent 2,528,092; *Chem. Abstr.* **45**, 1338h (1951).

<sup>329</sup> W. Braun and M. Bertl (Badische Anilin & Soda Fabrik A.-G.), French Patent 1,368,390; *Chem. Abstr.* **62**, 567b (1965).

10-Methylphenothiazine with acetic anhydride and  $\text{AlCl}_3$  gives only the 3,7-diacyetyl derivative,<sup>65</sup> and not a monoacyetyl derivative as earlier reported.<sup>330</sup> Scheme 10 shows the proof of structure of the diketone (106); 3,7-diethyl-10-methylphenothiazine (107) is obtained by reduction of 3,7-diacyetyl-10-methylphenothiazine (106), and also



SCHEME 11

by a sequence involving two consecutive Vilsmeier reactions, the substitution para to nitrogen in the latter reactions being well established.

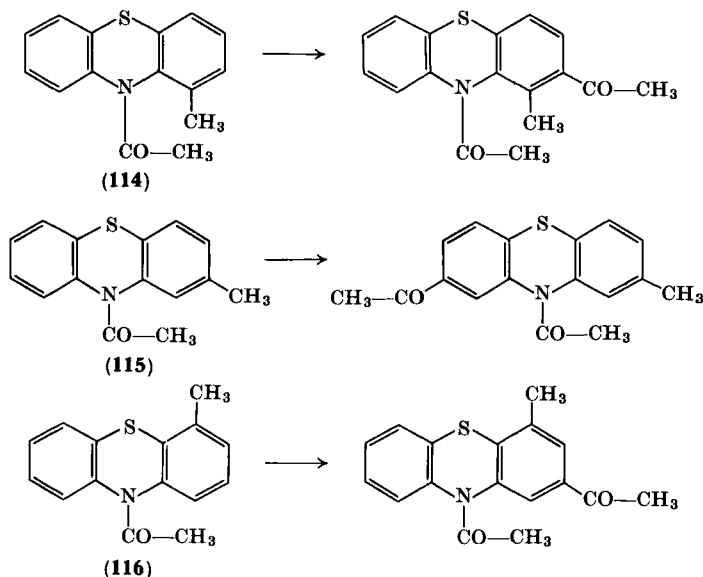
Attempts to prepare a monoketone also failed with 10-ethyl- and 10-phenylphenothiazine. There is evidence, derived primarily from UV spectra, that 2,7-diketones are the products when 3,10-dialkylphenothiazines undergo Friedel-Crafts acylation.<sup>65</sup> The best yields of diketones are obtained, as expected, when a 1:2 molar ratio of  $\text{AlCl}_3$  and acetic anhydride is used, because the catalyst is involved here only in the generation of the electrophilic agent of the Friedel-Crafts reaction, unlike with the 10-acyl derivatives where it also forms a complex 10-acylphenothiazine- $\text{AlCl}_3$ .<sup>331</sup>

<sup>330</sup> A. Burger and A. C. Schmalz, *J. Org. Chem.* **19**, 1841 (1954).

<sup>331</sup> G. Cauquil and A. Casadevall, *Compt. Rend.* **240**, 538 (1955).

10-Acylphenothiazines are acylated to 2,10-diacyl- and 2,8,10-triacylphenothiazines as proved by Cauquil and Casadevall<sup>332, 333</sup> (Scheme 11).

Because complexing with  $\text{AlCl}_3$  stabilizes the 10-acyl derivatives, Friedel-Crafts acylation may be used to introduce onto the ring other acyl residues than the one already present in position 10. Thus,



SCHEME 12

2-acetyl-10-formylphenothiazine can be prepared from 10-formylphenothiazine.<sup>331</sup> Profft and Kasper<sup>71</sup> thoroughly investigated the influence of the 10-acyl group upon the yield of pure 2,10-diacyl derivative, and concluded that optimal results are obtained when 10-chloroacetylphenothiazine is a starting material. Chlorobenzene was found to be the most convenient reaction medium.<sup>334</sup>

Many other authors have reported 2-acylation using aliphatic and unsubstituted and substituted aromatic acyl chlorides.<sup>71, 90, 150, 298.</sup>

<sup>332</sup> G. Cauquil and A. Casadevall, *Compt. Rend.* **238**, 908 (1954).

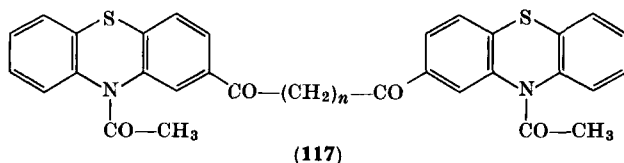
<sup>333</sup> G. Cauquil and A. Casadevall, *Bull. Soc. Chim. France*, 768 (1955)

<sup>334</sup> A. Georgiev, *Compt Rend. Acad. Bulgare Sci.* **17**, 267 (1964); *Chem. Abstr.* **61**, 8303b (1964).

<sup>335-339</sup> Because of its availability, 10-acetylphenothiazine was the most usual starting material. A parallelism between the yields and the electronegativities of the acyl groups of the chlorides was observed.<sup>90</sup>

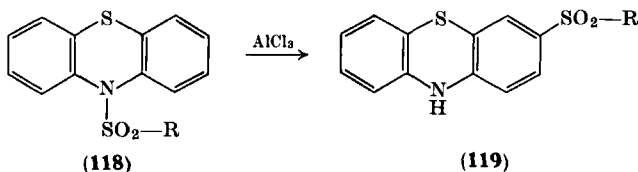
Bräuniger and Ahrend<sup>85-87</sup> investigated the orientation of electrophilic substitution in 10-acyl derivatives. They submitted the methyl 10-acetylphenothiazines **114-116** to Friedel-Crafts acylation and found the products of Scheme 12.

With 10-acylphenothiazines, the dichlorides of dicarboxylic acids gave 2,2'-diphenothiazinyldiketones (**117**)<sup>71</sup>; it was not possible to stop the reaction at the monoketone monoacid chloride stage. The longer the chain of the dicarboxylic acid, the greater are the yields of diketone.



A *C*-substituted product was formed on treating phenothiazine with ferrocene carboxylic acid chloride even in the absence of  $\text{AlCl}_3$ .<sup>340</sup>

Sulfur-containing groups have also been introduced into the benzene rings of phenothiazine under Friedel-Crafts conditions.



<sup>335</sup> G. Cauquil, E. Casadevall, and A. Casadevall, *Compt. Rend.* **243**, 159 (1956).

<sup>336</sup> M. Siska, L. Szporny, and O. Clauder, *Acta Pharm. Hung. Suppl.*, 91 (1961); *Chem. Abstr.* **56**, 7308c (1962).

<sup>337</sup> T. Ueda and J. Takada (Meito Sangyo Co. Ltd.), Japanese Patent 7483 (1962); *Chem. Abstr.* **59**, 1652h (1963).

<sup>338</sup> M. Siska, O. Clauder, F. Ruff, K. Magda, and J. Szegi, *Acta Pharm. Hung.* **35**, 272 (1965); *Chem. Abstr.* **64**, 6647d (1966).

<sup>339</sup> P. K. Kadaba, *J. Heterocyclic Chem.* **3**, 345 (1966).

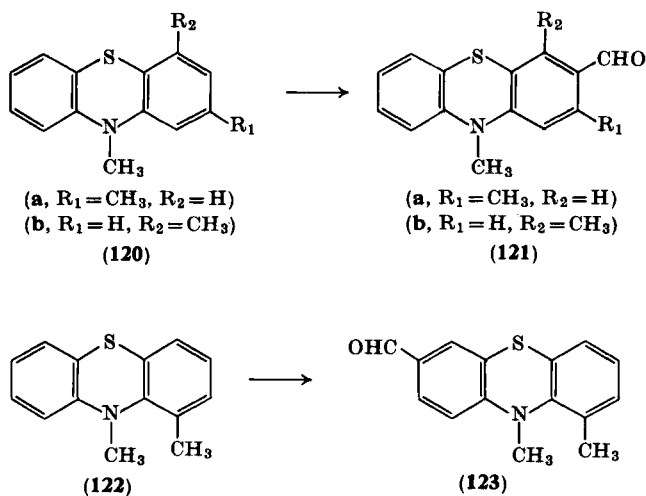
<sup>340</sup> E. M. Acton and R. M. Silverstein, *J. Org. Chem.* **24**, 1487 (1959).



Unexpectedly, phenothiazine with sulfonyl chlorides in the presence of  $\text{AlCl}_3$  yields only 3-monosulfonyl derivatives (119).<sup>68</sup> Probably, 10-sulfonyl derivatives (118) are intermediates which subsequently rearrange. 10-Sulfonyl derivatives are rearranged by  $\text{AlCl}_3$  into 3-sulfonyl derivatives, and 10-benzenesulfonylphenothiazine with tosyl chloride gives only 3-benzenesulfonylphenothiazine.

Dialkyl sulfides and aluminum chloride are reported to introduce alkylthio groups in position 3 of the phenothiazine molecule.<sup>341</sup>

Attempts to introduce the  $-\text{SCCl}_3$  group into the molecule of 10-methylphenothiazine failed.<sup>342</sup>



SCHEME 13

*d. Vilsmeier Formylation.* This reaction, first applied to phenothiazine by Buu Høi and Hoán,<sup>343</sup> was investigated in more detail by Cauquil and co-workers. *C*-Formylation of 10-alkyl- and 10-phenylphenothiazine occurs, whereas 10-acylphenothiazines undergo *N*-formylation with displacement of the acyl group except in the case of 10-benzoylphenothiazine.<sup>344</sup> The aldehyde groups always

<sup>341</sup> J. H. Mayer and J. Levy (Universal Oil Products Co.), U.S. Patent 3,136,762; *Chem. Abstr.* **61**, 4370c (1964).

<sup>342</sup> A. Senning, *Acta Chem. Scand.* **17**, 2570 (1963).

<sup>343</sup> Ng. Ph. Buu-Høi and Ng. Hoán, *J. Chem. Soc.*, 1834 (1951).

<sup>344</sup> G. Cauquil and A. Casadevall, *Compt. Rend.* **236**, 1569 (1953).

enter para to nitrogen<sup>345, 346</sup>; 3,10-dialkylphenothiazines are formylated only in position 7 and 3,7,10-trialkylphenothiazines cannot be converted into aldehydes by the Vilsmeier procedure. In 1,10-, 2,10-, and 4,10-dimethylphenothiazine there are two free positions para to nitrogen. The site of substitution in these compounds was determined by reduction to trimethyl derivatives; the latter were compared with authentic products. Thus it was found that the formyl groups enter the substituted ring when the methyl is located ortho to position 3, but the unsubstituted ring in 1,10-dimethylphenothiazine (Scheme 13).

### 5. Metalation

The early investigations of Gilman's school<sup>347, 348</sup> on the metalation of phenothiazines has recently been extended by Gilman and also by Cauquil *et al.*<sup>349, 350</sup>

Phenothiazine gives exclusively phenothiazine-1-carboxylic acid on treatment with butyllithium followed by carbonation; with 10-alkylphenothiazines the same reaction leads to a mixture of almost equal quantities of the 1- and 4-carboxylic acids. 10-Acylphenothiazines undergo deacylation in the metalation reaction, so that the same results are obtained as with *N*-unsubstituted phenothiazines.

When lithiated phenothiazine is treated with methyl sulfate, acetyl chloride, and ethylene oxide 10-substituted derivatives are obtained. Lithium salts of carboxylic acids, however, lead to 1-phenothiazinyl ketones; Scheme 14 presents the evidence for the structures assigned to these substances.

These findings suggest the intermediate formation of a 1,10-dilithio derivative, which reacts either in position 1 or 10 depending on the reagent. This is supported by the optimal yields of phenothiazine-1-carboxylic acid obtained by using 2 moles of butyllithium to 1 of

<sup>345</sup> G. Cauquil and A. Casadevall, *Compt. Rend.* **240**, 1784 (1955).

<sup>346</sup> G. Cauquil, E. Casadevall, and R. Greze, *Bull. Soc. Chim. France*, 590 (1964).

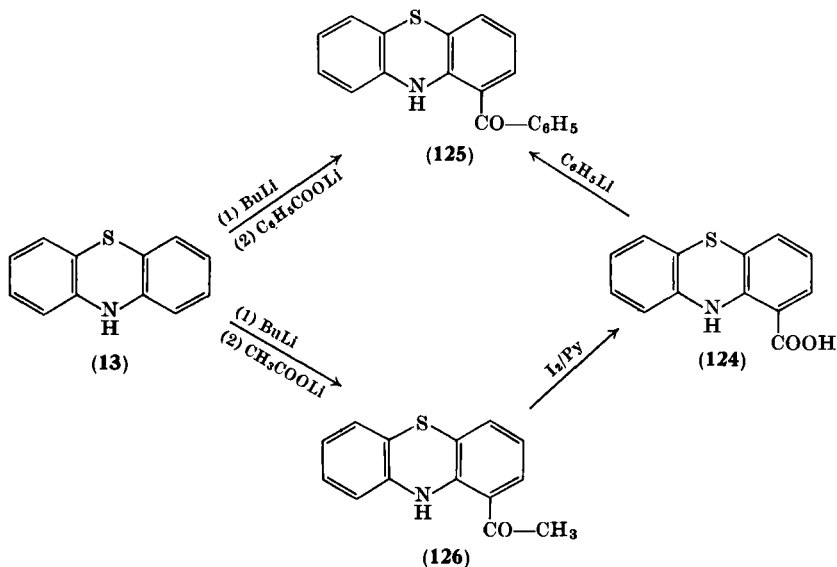
<sup>347</sup> H. Gilman, D. A. Shirley, and P. R. Van Ess, *J. Am. Chem. Soc.* **66**, 626 (1944).

<sup>348</sup> H. Gilman, P. R. Van Ess, and D. A. Shirley, *J. Am. Chem. Soc.* **66**, 1216 (1944).

<sup>349</sup> G. Cauquil, A. Casadevall, and E. Casadevall, *Compt. Rend.* **243**, 590 (1956).

<sup>350</sup> G. Cauquil, A. Casadevall, and E. Casadevall, *Bull. Soc. Chim. France*, 1049 (1960).

phenothiazine, and the fact that, on treatment with phenyllithium, phenothiazine is readily metalated in position 10, but not in 1. Metalation in position 1 requires the use of butyllithium and needs 30 hours for completion. The 10-lithio derivative does not rearrange into the 1 derivative because, when phenothiazine and butyllithium in a 1 : 1 molar ratio are reacted 30 hours, no 1-substituted derivative is obtained.



SCHEME 14

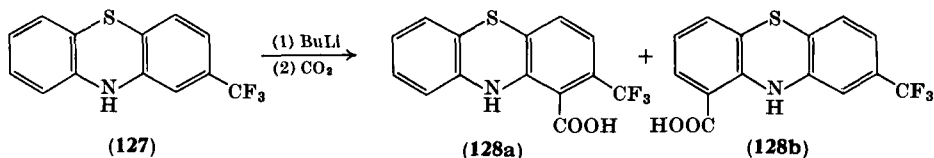
The reaction of 10-alkylphenothiazines with butyllithium followed by the action of reagents other than CO<sub>2</sub>, namely lithium salts of carboxylic acids, (CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub>, CH<sub>2</sub>O, ethylene oxide, or *N*-methyl formanilide, yielded 4-substituted derivatives in all cases, and the lithium carboxylates gave also a little of the 3-substituted phenothiazines.

10-Ethylphenothiazine-4-carboxylic acid was prepared in small yield on treating 10-ethylphenothiazine with triphenylsilyllithium and CO<sub>2</sub>.<sup>351</sup>

<sup>351</sup> H. Gilman, O. L. Marrs, W. J. Tropka, and J. W. Diehl, *J. Org. Chem.* **27**, 1260 (1962).

Metalation of *C*-substituted phenothiazines has been recently reported.<sup>352</sup> It is of interest that 2-trifluoromethylphenothiazine (**127**) is metalated in both ortho positions with respect to nitrogen, that is, in 1 and 9.

The preparative value of metalation reactions consists primarily in the possibility of obtaining 1- and 4-substituted phenothiazines, which are difficult to prepare by other methods. Also lithiation at position 3 by halogen-metal exchange using triphenylsilyllithium<sup>99</sup> presents interesting possibilities.

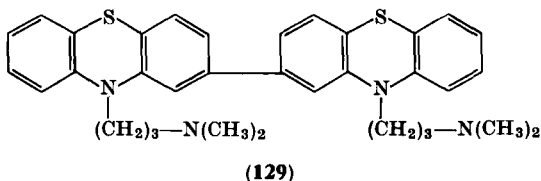


#### 6. *C*-Substitution by Replacement of Halogen

The replacement of halogens by other halogens and by nitro groups was discussed in Sections V, A, 1 and V, A, 2.

2-Cyanophenothiazine has been obtained by the action of CuCN upon 2-chlorophenothiazine.<sup>353, 354</sup>

Chlorpromazine undergoes a Wurtz condensation on passing through a column filled with pyrophoric lead, giving bispromazine (**129**) in 90% yield.<sup>355</sup>



<sup>352</sup> Smith Kline & French Laboratories, Netherland Appl. 6,514,994; *Chem. Abstr.* **65**, 15393c (1966).

<sup>353</sup> Société des Usines Chimiques Rhône-Poulenc, French Patent 1,186,196; *Chem. Abstr.* **55**, 19964h (1961).

<sup>354</sup> Knoll A.-G. (Chemische Fabriken), British Patent 903,725; *Chem. Abstr.* **58**, 5697f (1953).

<sup>355</sup> L. Meszaros, Hungarian Patent 152,090; *Chem. Abstr.* **63**, 9960c (1965).

Triphenylsilyllithium converted 2-, 3-, and 4-halogeno-10-ethylphenothiazines into the corresponding triphenylsilyl derivatives,<sup>99</sup> and, in the same way, impure bistrisphenylsilyl derivatives have been obtained from 3,7-dichloro- and 3,7-dibromo-10-ethylphenothiazines.

A Grignard reaction has been used to convert 3-bromo-10-ethylphenothiazine into 10-ethylphenothiazine-3-carboxylic acid.<sup>247</sup>

The preparation of some 2-chloro-3,7-bis(3-carbamoyl-1-pyridyl)phenothiazines by the action of nicotinamide upon the products of bromination of 2-chlorophenothiazine and of its *N*-substituted derivatives is described in a patent.<sup>356</sup>

Bodea *et al.*<sup>236, 255</sup> removed the bromine atoms from positions 1, 2, 8, and 9 of halogenophenothiazines by zinc in acetic acid. 2-Chlorophenothiazine is dechlorinated by lithium in tetrahydrofuran.<sup>357</sup>

### 7. Ring Cleavage Reactions

There are many cleavage reactions of the phenothiazine heterocycle which may be interpreted as substitutions at the carbon atom adjacent to sulfur. These reactions depend to a great extent upon the oxidation state of sulfur; they occur with phenothiazines and phenothiazine-5-oxides, but not with the 5,5-dioxides. In structure proofs such cleavage reactions are of particular importance, because they often lead to diphenylamines with known structures.

No reactions in which C—N bonds of the phenothiazine ring are selectively broken have been reported.

The action of lithium in dioxan or tetrahydrofuran cleaves only one C—S bond, the final product of the reaction being a 2-mercaptodiphenylamine, when the reaction is completed by a carbonation.<sup>358</sup> If the reaction with lithium is followed by a hydrolysis, diphenylamine is formed as a by-product, owing to a partial desulfurization.

*N*-Substituted 2-mercaptodiphenylamines are obtained under the conditions of the Birch–Wilds reaction ( $\text{Li} + \text{EtOH/liq. NH}_3$ ) from phenothiazines carrying ethyl or dialkylaminoalkyl residues in position 10, without hydrogenation of the benzene rings.<sup>359</sup>

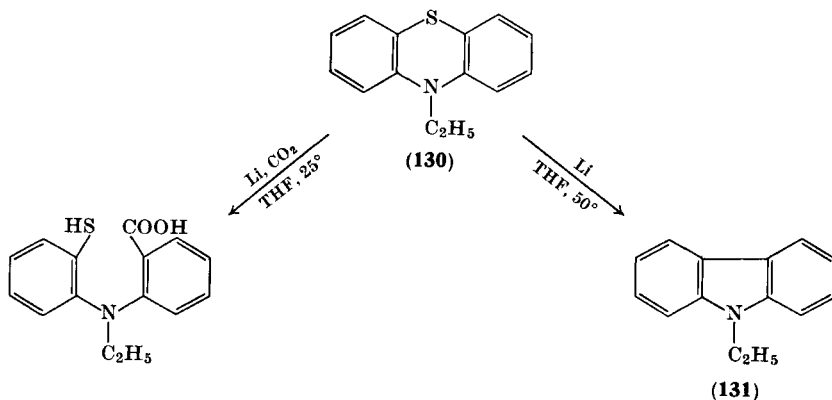
<sup>356</sup> M. Cholodny, Israeli Patent 9399; *Chem. Abstr.* **52**, 2093b (1958).

<sup>357</sup> H. Gilman and J. J. Dietrich, *J. Am. Chem. Soc.* **80**, 380 (1958).

<sup>358</sup> H. Gilman, J. B. Honeycutt, Jr., and R. K. Ingham, *J. Org. Chem.* **22**, 338 (1957).

<sup>359</sup> M. Suquet and J. Schmitt, *Bull. Soc. Chim. France*, 2113 (1960).

The treatment of 10-ethyl- (130) and 10-phenylphenothiazine with lithium in tetrahydrofuran at 25° leads after carbonation to the corresponding *N*-substituted 2-mercapto-2'-carboxydiphenylamine. At 50°, 9-ethylcarbazole (131) is obtained from (130).<sup>357</sup>



It may appear surprising that, as mentioned above, 2-chlorophenothiazine does not undergo ring cleavage upon reaction with lithium in tetrahydrofuran, when there is only replacement of chlorine by hydrogen.<sup>357</sup> This is due to the formation of a 10-lithio derivative, resulting in protection against ring cleavage. It was shown that after reaction of 2-chlorophenothiazine with phenyllithium, when the 10-lithio derivative is formed (Section V, A, 5), treatment with an excess of metallic lithium leads only to phenothiazine, without ring opening.

Dahlbom<sup>360</sup> reported that  $\text{LiAlH}_4$  does not lead to cleavage reactions, and this was confirmed by Zhuravlev and Gritsenko.<sup>73</sup>

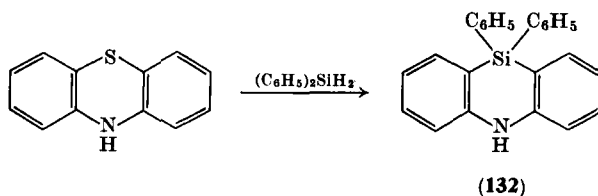
Raney nickel was recommended as a convenient reagent for desulfurization of phenothiazine, and it has been used in many structural investigations.<sup>361</sup> More recently, the method has been applied to various phenothiazines,<sup>85, 316, 349, 350</sup> in its classical form, that is Raney nickel and hydrogen, as well as in some modified variants. Thus, working with a "special" Raney nickel, without hydrogen, 1,3,7,9-tetrachlorophenothiazine was desulfurized without dehalogenation<sup>290</sup>; the usual procedure leads, for example, to diphenylamine, when applied to 3,7-dichlorophenothiazine.<sup>153</sup>

<sup>360</sup> R. Dahlbom, *Acta Chem. Scand.* **6**, 310 (1952).

<sup>361</sup> R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.* **68**, 2673 (1946).

The desulfurizing action of HI, well known from both early<sup>2</sup> and recent work,<sup>60</sup> is surprisingly absent when this reagent acts upon 10-ethylphenothiazine; only the ethyl residue is removed. 10-Ethyl- and 10-phenylphenothiazine-4-carboxylic acids are desulfurized under these conditions; in the case of the former the ethyl group is also removed.<sup>358</sup> The greater the concentration of the hydriodic acid, the easier is the ring opening.<sup>247</sup>

Gilman and Wittenberg<sup>362</sup> described the replacement of sulfur from phenothiazine and 10-ethylphenothiazine by the diphenylsilyl group, giving **132**, on reaction with diphenylsilane.



## B. N-SUBSTITUTION

As mentioned in Section I, only new methods for the introduction of substituents in position 10 and *N* derivatives with particular structures will be dealt with here.

### 1. Alkylations

*a. With Halides.* The classical route to *N*-alkylphenothiazines (condensation with alkylchlorides in the presence of a basic agent) has developed some variants in recent years.

Thus, almost quantitative yields of *N*-alkylphenothiazines are claimed on heating phenothiazine and alkylchlorides in benzene without catalysts.<sup>363</sup> In the presence of potassium ethoxide in dimethylformamide, alkyl chlorides can even alkylate 5-oxides, e.g., 2-chlorophenothiazine-5-oxide.<sup>364</sup> However, the lowering of the reactivity in *N*-substitution reactions by oxidation at sulfur is obvious: with ethyl bromide and sodamide in liquid ammonia the

<sup>362</sup> H. Gilman and D. Wittenberg, *J. Am. Chem. Soc.* **79**, 6339 (1957).

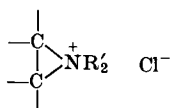
<sup>363</sup> A. Smith (Cassella Farbwerke Mainkur Akt.-Ges.), German Patent 922,467; *Chem. Abstr.* **52**, 5485h (1958).

<sup>364</sup> Société des Usines Chimiques Rhône-Poulenc, French Patent 1,167,653; *Chem. Abstr.* **55**, 9436g (1961).

yield of 10-ethylphenothiazine-5-oxide is 7% whereas that of 10-ethylphenothiazine is 98–99%.<sup>247</sup>

The favorable influence of a hexamethylphosphotriamide (hexametapol) medium upon a variety of reactions with ionic mechanism is shown by the *N*-methylation of phenothiazine with  $\text{CH}_3\text{I}$  in the presence of basic condensing agents. Very good yields of 10-methylphenothiazine have thus been obtained.<sup>365, 366</sup>

10-Dialkylaminoalkylphenothiazines may be prepared replacing the usual condensating agent, sodamide, by an excess of sodium hydroxide. In the case of alkyl or haloalkyl halides the *N*-substitution of phenothiazine in the presence of sodium hydroxide fails. The formation of intermediate cyclic quaternary ammonium salts (133) from the dialkylaminoalkyl halides was suggested to explain this effect. Quaternary ammonium salts appear to catalyze the condensation of alkyl halides with phenothiazine in the presence of  $\text{NaOH}$ .<sup>367</sup>



(133)

Unexpectedly, 3-bromopropyne does not react with phenothiazine under the usual conditions (sodamide, xylene), but yields *N*-(1-propynyl)phenothiazine (70% yield) (134) instead of the 2-propynyl isomer (135), when the reaction is carried out in dimethylformamide with sodium hydride.

Structure 134 was proved by IR spectra. The existence of a dipolar ion  $^+\text{CH}_2\text{---C}\equiv\text{C}^- \leftrightarrow ^-\text{CH}_2\text{---C}\equiv\text{C}^+$  which is more readily attacked by nucleophilic reagents at the acetylenic carbon might account for the somewhat unusual course of the reaction.<sup>368</sup>

*b. With Alkenes, Alkene Oxides, and Alkynes.* In a study of the reactions of nucleophiles with fluoroolefins, England *et al.*<sup>369</sup>

<sup>365</sup> H. Normant and T. Cuvigny, *Bull. Soc. Chim. France*, 1866 (1965).

<sup>366</sup> H. Normant, T. Cuvigny, J. Normant, and B. Angelo, *Bull. Soc. Chim. France*, 3446 (1965).

<sup>367</sup> H. Wunderlich, W. Lugenheim, A. Stark, and G. Detrekoei, *Pharmazie* **21** 57 (1966).

<sup>368</sup> H. E. Zaugg, L. R. Swett, and G. R. Stone, *J. Org. Chem.* **23**, 1389 (1958).

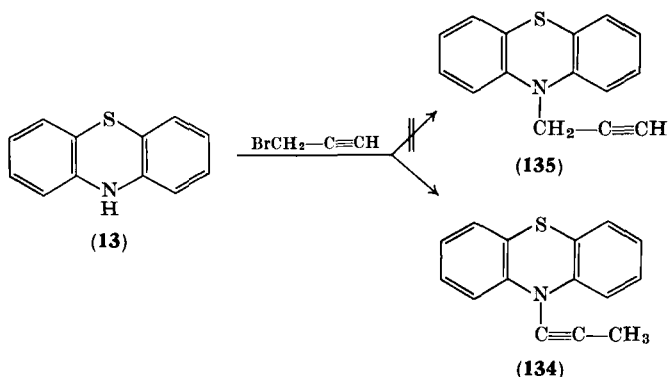
<sup>369</sup> D. C. England, L. R. Melby, M. A. Dietrich, and R. V. Lindsey, *J. Am. Chem. Soc.* **82**, 5116 (1960).



observed 10-tetrafluoroethylation of phenothiazine by tetrafluoroethylene.

The preparation of 10-(2-hydroxyalkyl)phenothiazines from alkene oxides and phenothiazines in the presence of bases is described in a patent.<sup>370</sup> Conditions were subsequently found under which *N*-polyoxyalkylene derivatives of phenothiazine and phenothiazine-5-oxide may be obtained using the same reagents.<sup>371</sup>

Reppe *et al.*<sup>372</sup> prepared *N*-vinylphenothiazine from acetylene and phenothiazine in cyclohexane in the presence of catalysts.



*c. With Esters.* Tosylates have been successfully used as alkylating agents. Simov Antonov<sup>248</sup> methylated 3,7-dichlorophenothiazine with methyl tosylate in chlorobenzene, a reaction which cannot be performed using methyl iodide. Even 3,7-dichlorophenothiazine-5,5-dioxide was methylated by TsOMe.<sup>259</sup> It was possible to prepare 10-dialkylamino-alkylphenothiazines in moderate yield using the corresponding tosylates instead of the halides (sodamide, xylene).<sup>373</sup> The alkylation with dialkylaminoalkyltosylates has been extended to 2-acylphenothiazines.<sup>374</sup> Owing to the poor stability of these tosylates, the method

<sup>370</sup> R. Dahlbom (Aktiebolaget Astra Apotekarnes Kemiska Fabriker), Swedish Patent 129,843; *Chem. Abstr.* **45**, 5193e (1951).

<sup>371</sup> L. H. Horsley and H. O. Seeburger (Dow Chemical Co.), U.S. Patent 2,815,343; *Chem. Abstr.* **52**, 6415d (1958).

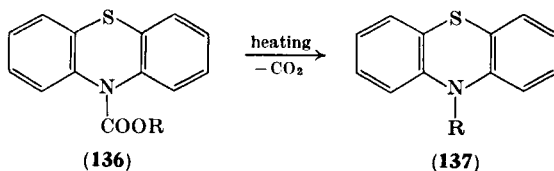
<sup>372</sup> W. Reppe and co-workers (Badische Anilin- und Soda Fabrik A.G.), *Ann. Chem.* **601**, 128 (1956).

<sup>373</sup> K. Fujii, *J. Pharm. Soc. Japan* **76**, 637 (1956).

<sup>374</sup> J. Schmitt, A. Hallot, P. Comoy, M. Suquet, R. Fallard, and J. Boitard, *Bull. Soc. Chim. France*, 1474 (1957).

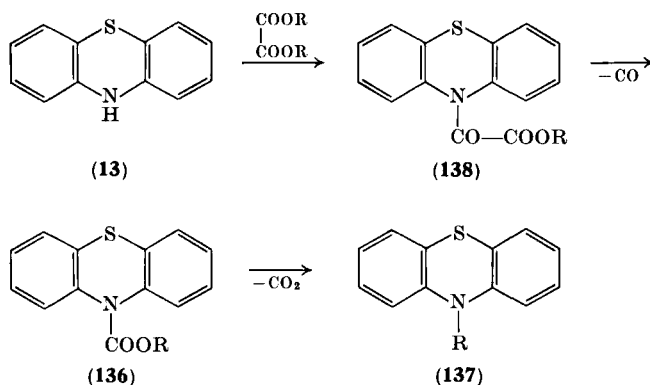
is not of much practical use. The use of ethoxycarbonyloxy derivatives of dialkylamino alcohols for the same purposes has also been reported.<sup>375</sup>

Schmitt *et al.*<sup>150</sup> worked out an interesting procedure, applicable on a large scale, for introducing alkylaminoalkyl residues in position 10, via the esters of phenothiazine-10-carboxylic acid (**136**). On thermal decomposition, the latter eliminate  $\text{CO}_2$  and give the deri-



vatives **137**. When  $\text{R}$  is a branched-chain group, this reaction is accompanied by isomerization.<sup>374</sup>

The esters of phenothiazine-10-thiocarboxylic acid undergo a similar thermal decomposition yielding 10-dialkylaminoalkylphenothiazines and  $\text{COS}$ ; however, they are more stable than their oxygen analogs, and the reaction therefore needs more severe conditions, so that the yields are lower owing to the formation of resinous by-products.<sup>374</sup>

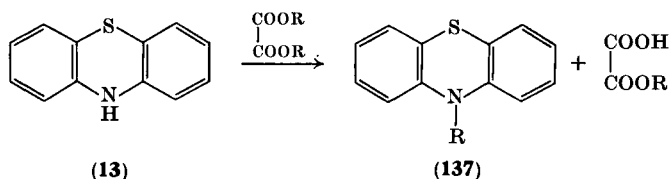


SCHEME 15

<sup>375</sup> I. Fabricius (Novo Terapeutisk Laboratorium A/S), Belgian Patent 620,485; *Chem. Abstr.* **59**, 7536h (1963).

Lespagnol<sup>376</sup> prepared *N*-alkylphenothiazines using oxalic esters. In this reaction, the formation of 10-alkoxalylphenothiazines (**138**) is expected since esters usually convert secondary amines into amides. It might be supposed that **138** is thermally decomposed in a way similar to the phenothiazine-10-carboxylate esters (**136**), the decarboxylation being here accompanied by decarbonylation, a common occurrence with oxalyl derivatives (Scheme 15).

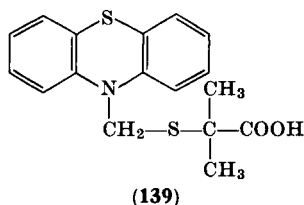
The author, however, found that, under the experimental conditions, the two suggested intermediates **138** and **136** are stable; consequently, it appears that direct alkylation takes place here (Scheme 16).



SCHEME 16

*d. With Other Alkylating Agents.* The introduction of a  $\beta$ -(aminooxy) ethyl ( $-\text{CH}_2\text{CH}_2\text{ONH}_2$ ) radical in position 10 by means of *O*-(2-tosyloxyethyl)acetooxime has been reported by Paquette.<sup>377</sup>

Buttini *et al.*<sup>378</sup> claimed that **139** is formed from phenothiazine,  $\alpha$ -thioisobutyric acid, and formaldehyde. Confirmation of this



*N*-substitution would seem to be desirable, because formaldehyde in acid media condenses, as in diphenylamine, para to the nitrogen atom

<sup>376</sup> C. Lespagnol, *Bull. Soc. Chim. France*, 112 (1960).

<sup>377</sup> L. A. Paquette, *J. Org. Chem.* **29**, 3545 (1964).

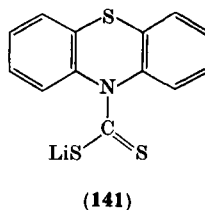
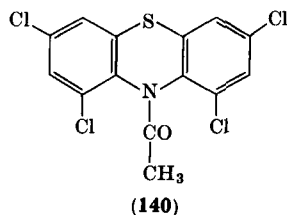
<sup>378</sup> A. Buttini, M. Melandri, G. M. Carminati, and P. Galimberti, *Boll. Chim. Farm.* **103**, 414 (1964); *Chem. Abstr.* **61**, 9496e (1964).

(see Section V, A, 4, b). The introduction of the 9-xanthenyl residue in position 10 of phenothiazine by refluxing the latter with xanthidrol in acetic acid has been reported.<sup>379</sup>

## 2. Acylation

By condensation of acyl chlorides with phenothiazines, numerous new *N*-acylphenothiazines have been prepared recently, including, for example, the ferrocenoyl derivative.<sup>340</sup>

*N*-Acylation is, of course, rendered more difficult by the presence of substituents in positions 1 and 9, owing to steric effects. Massie and Kadaba<sup>98</sup> observed that 1-substituted derivatives may be acetylated with acetic anhydride in pyridine, but the use of anhydrous solvents throughout the synthesis and purification is required, since the products are very readily hydrolyzed. 1-Chloro-10-acetylphenothiazine, for example, loses its acyl group even on pouring the reaction mixture into water. Isopropenyl acetate has been recommended by the same authors<sup>379</sup> as an acetylating agent which is able to overcome the steric hindrance in 1-substituted phenothiazines.



Spasov and Panov<sup>301</sup> reported that  $P_2O_5$  as a condensating agent yields an *N*-acetyl derivative (140) even from 1,3,7,9-tetrachlorophenothiazine, a substance which is not only of low reactivity but also characterized by strong steric hindrance to 10-substitution.

Carbon disulfide and lithium converted phenothiazine into the lithium salt of phenothiazine-10-carbodithioic acid (141).<sup>380</sup>

Sulfonyl chlorides yield 10-sulfonyl derivatives.<sup>68, 381</sup>

<sup>379</sup> P. K. Kadaba and S. P. Massie, *J. Org. Chem.* **24**, 986 (1959).

<sup>380</sup> Société des Usines Chimiques Rhône-Poulenc, French Patent 1,186,819; *Chem. Abstr.* **56**, 479g (1962).

<sup>381</sup> L. Almási and N. Serban, *Studii Cercetari Chem. (Cluj)* **7**, 141 (1956); *Chem. Abstr.* **52**, 12871g (1958).

### 3. Other *N*-Substitution Reactions

There is a report of the formation of a compound believed to be 10,10'-dithiodiphenothiazine, by the action of  $S_2Cl_2$  upon phenothiazine<sup>382</sup> (cf., however, Section V, A, 1, *d*).

Bis(10-phenothiazino)dibutylstannonium dilaurate has been prepared by heating dibutyltin dilaurate with phenothiazine.<sup>383</sup>

*In vivo* hydrolysis of 10-formylphenothiazine to phenothiazine has been claimed to account for the anthelmintic action of the formyl derivative.<sup>149</sup>

## C. A GENERAL OUTLINE OF THE SUBSTITUTION REACTIONS OF THE PHENOTHIAZINE RING

The numerous examples of the preceding sections have emphasized the versatility of the chemical reactivity of the phenothiazine ring. The introduction of groups at different positions affects profoundly and in a rather complicated manner both the orientation of substitution and the overall reactivity. The existing material is, however, sufficient to allow a systematization of the phenothiazine substitution data.

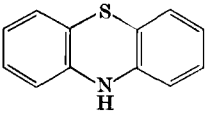
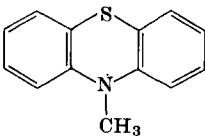
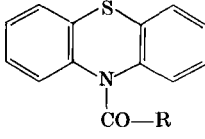
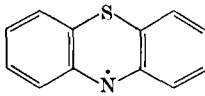
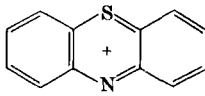
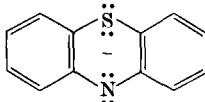
The reasons for the difficulty in prediction of the pathway a substitution reaction will follow are, of course, to be looked for in the peculiarities of the phenothiazine ring structure. To form this heterocyclic system, two benzenic rings are linked together by a sulfide and an imine bridge, located ortho with respect to each other. The inductive and conjugative effects of the two heteroatoms may thus fully interact; at the same time, along with the two quinonoid and four *o*-quinonoid systems each heteroatom can generate with the electronic systems of the two benzene rings, two *o*-quinonoid forms involving mainly the central thiazine ring may be formed. The importance of these features is strikingly brought out in the chemical behavior of oxidized forms, as is shown in Section IV, G. As a consequence of these structural-electronic features, although phenothiazine is not strictly a heteroaromatic compound,<sup>384</sup> the transmission

<sup>382</sup> R. O. Zerbo (Monsanto Chemical Co.), U.S. Patent 2,659,724; *Chem. Abstr.* **48**, 2406c (1954).

<sup>383</sup> E. L. Weinberg (Metal and Thermit Corp.), U.S. Patent 2,867,566; *Chem. Abstr.* **53**, 17441f (1959).

<sup>384</sup> A. Albert, "Heterocyclic Chemistry," p. 290. Oxford Univ. Press (Athlone), London and New York, 1959.

TABLE VII  
SUBSTITUTION IN THE PHENOTHAIAZINE RING

Group	Typical compound	Electrophilic substitution	Nucleophilic substitution <sup>a</sup>
<i>N</i> -Unsubstituted phenothiazines		N-10 C-3,7 > C-1,9 > C-2,8 > C-4,6	C-(4,6,2,8) > C-1,9 > C-3,7
"Slightly deactivated" phenothiazines		C-3,7 > C-1,9	C-1 and C-4
"Strongly deactivated" phenothiazines		C-2 and C-8 (N-10)	—
Phenothiazinyl free radicals		Dimerization N-10, N-10'; C-3, N-10'; C-3, C-3'	
Phenazathionium cations		—	S-5 C-3 and C-7
Phenazathionium anions		N-10	C-1

<sup>a</sup> Including metalation.

of electronic effects from one point of the molecule to the other is very efficient, but often surprising modification of the relative reactivities of the different positions occur. A further source of complication is the existence of the two configurations "extra" and "intra" which may be adopted by the —NH— group (see Sections III, A, 2 and IV, D). Because these configurations are not electronically

equivalent, interaction between steric and electronic effects is to be expected in phenothiazine chemistry, and indeed appears to take place. In conclusion, it should be remembered that, even when compared with closely related heterocycles like phenoxazine, phenothiazine is a somewhat unusual system, in that the sulfur atom can use its  $3d$  orbitals in bonding. The extent to which this actually occurs, in phenothiazine as elsewhere, is a still unsettled question.

So far as the relative influence of the two heteroatoms upon the chemical reactivity is concerned, it appears that in phenothiazine chemistry it is the nitrogen which usually plays the key role, although the influence of the sulfur atom is very important, and occasionally dominates. This occurs, for example, with *N*-acylated phenothiazines, when the involvement of the nitrogen in an amide group greatly curtails its orientating power in substitution reactions. The relative importance of nitrogen and sulfur is also underlined by the extent to which these two heteroatoms are involved in the structural differences existing between the six groups of phenothiazine compounds which may be distinguished on the basis of their behavior in substitution reactions (see Table VII).

### 1. *N*-Unsubstituted Phenothiazines

Except for highly halogenated and nitrated derivatives, compounds of this type are very reactive.

*a. Electrophilic Substitutions.* The highest electron density is located at the heterocyclic nitrogen atom owing to its relatively high electronegativity; consequently, many electrophilic reagents preferentially attack the phenothiazine ring in position 10, yielding a variety of acyl, alkyl, and other derivatives. *C*-Substitution also very readily takes place, positions 3 and 7 (para to nitrogen) being the first occupied, followed by 1 and 9 (ortho to nitrogen), then by 2,8 and 4,6 (respectively, para and ortho to sulfur). The 5-oxides and 5,5-dioxides of unsubstituted phenothiazine display a markedly reduced reactivity, but the order in which the positions are substituted is the same (see, for example, Sections V,A,1 and V,A,2).

*b. Nucleophilic Substitutions.* The only authentic nucleophilic substitution so far reported in the *N*-unsubstituted phenothiazines is the replacement of halogens by other groups. There is sufficient evidence, primarily derived from the work on reductive dehalogenation (see

Section V,A,6), to suggest that the order of reactivity of the different positions of the ring in nucleophilic substitutions is the reverse of that given above for electrophilic substitutions.

## 2. "Slightly Deactivated" Phenothiazines

*N*-Methylphenothiazine is a representative compound of this group which comprises phenothiazines carrying an alkyl or substituted alkyl group at the 10-nitrogen atom. These substances do not display the expected enhanced reactivity toward electrophilic reagents, as compared to *N*-unsubstituted phenothiazines. In fact, reactivity is reduced, for the reasons discussed in Sections III,A,2 and IV,D. The reduction, in *N*-substituted phenothiazines, of the participation of the nitrogen lone pair in the extended  $\pi$  system of the molecule, is a particular case of sterically hindered conjugation, leading to decreased reactivity in electrophilic substitutions. For example, no condensation with formaldehyde occurs with *N*-methylphenothiazine, even in the presence of HCl, whereas phenothiazine yields polymeric condensation products in acetic acid at room temperature. The reactivity toward the electrophiles (e.g., Br<sub>2</sub>) which first oxidize the phenothiazines to phenazathionium cation and then substitute via nucleophilic attack is also decreased. This is due to the increase in the redox potential of the phenothiazine—another consequence of the restricted conjugation.

*a. Electrophilic Substitutions.* Positions 3 and 7 are first attacked by electrophilic reagents; nitration, Friedel–Crafts acylation, Vilsmeier formylation, and other reactions (see Section V,A) yield always 3-mono- or 3,7-disubstituted products. In cases when the electrophilic mechanism is expected to operate, because of ring substituents increasing significantly the redox potential, thus rendering the oxidation to cation unfavored, e.g., bromination of 3-chloro-7-nitro-10-methylphenothiazine (Section V,A,1,*b*), substitution in position 1 or 9 without removal of the *N*-methyl group is possible. In other reactions, like bromination of 3,7-dibromo-10-methylphenothiazine (Section V,A,1,*b*) and reductive halogenation of 3,7-dichloro-10-methylphenothiazine-5-oxide (Section IV,G,4), when the intermediacy of the phenazathionium cation is very probable, no *C*-trisubstituted phenothiazine is obtained, but one gets directly the tetrasubstituted derivative with removal of the alkyl residue from position 10.



*b. Nucleophilic Substitutions.* Metalation was claimed in earlier literature<sup>2</sup> to proceed as expected only in position 4, where there is the lowest electron density. More recent work has shown (see Section V,A,5) that, in fact, metalation of 10-alkylphenothiazines occurs in both 1 and 4 positions, but that only CO<sub>2</sub> is a reagent of sufficiently small volume to overcome the steric hindrance exerted by the 10-alkyl group on 1-substitution; a mixture of 10-alkyl-1- and 10-alkyl-4-carboxylic acids is thus formed. With other reagents only the 4-substituted derivatives are obtained. The reason why metalation of 10-alkylphenothiazines occurs also in position 1 is still unaccounted for (see also Section V,C,6).

### 3. "Strongly Deactivated" Phenothiazines

*N*-Acylphenothiazines are considered here. The involvement of the nitrogen lone pair in amide conjugation results as expected in a considerable decrease in reactivity toward electrophilic reagents. This is utilized in those reactions when protection against ring substitution is required (e.g., conversion of less substituted phenothiazines into 5-oxides or 5,5-dioxides and preparation of acid chlorides of phenothiazine carboxylic acids), and when increased stability against oxidation must be ensured (e.g., in the case of the aminophenothiazines).

*a. Electrophilic Substitution.* Friedel-Crafts acylation leads to 2- and 2,8-substituted phenothiazines (that is, para to sulfur), showing that sulfur predominates here in orientating the substitution (see Section V,A,4,c). However, in Vilsmeier formylation, where there is no involvement of the 10-acyl group in AlCl<sub>3</sub>-complex formation, the electrophilic agent attacks at nitrogen, yielding *N*-formylphenothiazines (see Section V,A,4,d).

*4. Nucleophilic Substitution.* Almost nothing is known: no 10-acyl residue appears to be able to resist the deacylation which precedes metalation.

### 4. Phenothiazinyl Free Radicals

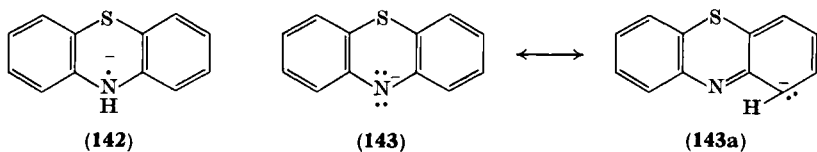
The only substitution reactions possible with these highly reactive, unstable compounds are the "oxidative couplings" leading to 10,10', 3,10', and 3,3'-biphenothiazines, considered in detail in Section IV,G,1.

### 5. Phenazathionium Cations

A review of the nucleophilic substitutions involving phenazathionium cations is given in Section IV, G. No electrophilic substitution of the cation has yet been reported; of course, such reactions would be very difficult to perform, because of the great tendency of the cation to give nucleophilic substitutions and because its cationic nature significantly decreases the reactivity toward electrophiles. However, the fact that electrophilic substitutions, if any, are expected to occur at other positions than the "classical" 1, 3, 7, and 9 might be of interest from the synthetic point of view.

### 6. Anions Derived from Phenothiazine

There are two kinds of anionic forms derived from phenothiazines: the radical anion **142** formed when an electron is forced onto the



phenothiazine ring by strong electron donors, like alkaline metals (see Section IV, F), and the anion **143** obtained by deprotonation at position 10. Only the second is of interest from the substitution point of view. The anion **143** is formed either by the action of usual basic reagents (alkali metal, amide, hydride, or hydroxide) or by a proton-metal exchange with an organometallic compound (Grignard reagent or organolithium).

*a. Electrophilic Substitutions.* Because of the high electron density at the negatively charged nitrogen, the anion gives substitution reactions even with unreactive electrophiles like alkyl and dialkyl-aminoalkyl halides. Many of the *N*-substitutions leading to pharmacologically important substances belong to this group.

*b. Nucleophilic Substitutions.* Although negatively charged, the anion **143** is still a stronger acid than an alkane: butyllithium is able to extract a second proton from *N*-lithiophenothiazine, giving a dilithio derivative (see Section V, A, 5). Since either 1-substituted or 10-substituted derivatives are obtained on work-up of dilithiophenothiazine, these positions are assumed to carry the metal atoms. Sulfur usually has a greater activating action in metalation reactions,

so that abstraction of the second proton from position 4 would be expected (cf. Section V, C, 2). The fact that the anion **143** may also be written in the *o*-quinonoid resonant form (**143a**) with high electron density at position 1 makes the metalation at C-1 still more surprising. Formation of a cyclic complex between *N*-lithiophenothiazine and a molecule of butyllithium, resulting in steric favoring of attack at the neighboring C-1 atom, might account for these facts. But the same phenomenon would then be expected to occur with unsubstituted phenoxazine, which is, in contrast, metalated as expected in position 4. Metalation at a position ortho or peri to nitrogen was also encountered in a series of benzophenothiazines by Shirley and co-workers.<sup>385-388</sup> Clearly, the metalation of *N*-unsubstituted phenothiazines is a case of departure from the usual rules.

## VI. Modifications of the Substituents in Phenothiazine Derivatives

The selection of the material dealt with in this section has been made on the basis of two criteria: (i) to what extent the reactivity of a substituent is influenced by the phenothiazine ring and (ii) the preparative value of a given reaction as a route to important phenothiazine derivatives.

### A. ALKYL AND SUBSTITUTED ALKYL GROUPS

There are relatively few papers on reactions of alkyl and related groups linked to the benzene rings, as compared to the studies devoted to the modifications of similar substituents in position 10.

#### 1. *C-Alkylphenothiazines and Related Derivatives*

On treating toluidine blue (**144**) with thionyl chloride, not only does ring chlorination take place, but also the 2-methyl is converted into a chloromethyl group (**145**).<sup>295</sup>

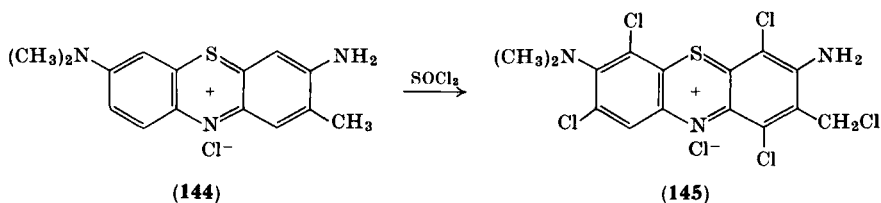
A series of 10-substituted 2-alkenyl- and 2-alkynyl phenothiazines underwent hydrogenation in the presence of Pd/C to give the corresponding saturated compounds.<sup>67, 92</sup>

<sup>385</sup> D. A. Shirley and J. C. Liu, *J. Org. Chem.* **25**, 1189 (1960).

<sup>386</sup> D. A. Shirley and W. E. Tatum, *J. Org. Chem.* **25**, 2238 (1960).

<sup>387</sup> D. A. Shirley and J. C. Gilmer, *J. Org. Chem.* **27**, 4421 (1962).

<sup>388</sup> D. A. Shirley and J. C. Goan, *J. Organometal. Chem. (Amsterdam)* **2**, 304 (1964).



## 2. *N*-Alkylphenothiazines and Related Derivatives

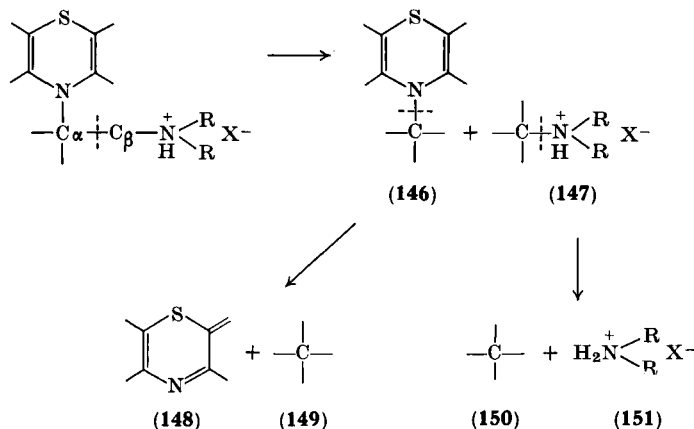
In a study of the stability of phenothiazine drugs carrying dialkylaminoalkyl groups in position 10, fission of the side chain was investigated. The number of carbon atoms between the heterocyclic nitrogen and the dialkylamino group was shown to determine the fate of the side chain.

*a. Two Carbon Atoms.* This is a characteristic feature of the parasympatholytic and antihistaminic phenothiazine drugs. Rupture of the side chain takes place with a variety of oxidants, the ring being oxidized to phenothiazone and other quinonoid compounds, so that permanent colorations appear. Side chain branching has practically no effect; therefore, it appears that the fragmentation of the side chain is not preferentially initiated by an attack at a tertiary carbon atom.

There is evidence that the first bond fission occurs between C- $\alpha$  and C- $\beta$  of the side chain (see Scheme 17). Thus, Waaler<sup>389</sup> decomposed promethazine hydrochloride by boiling water. In this case, only the nonheterocyclic fragment (147) is oxygenated; further degradation of the latter gives acetaldehyde (denoted here by 150) and dimethylamine hydrochloride (151, R = CH<sub>3</sub>, X = Cl). The heterocyclic fragment (146) represents 10-methylphenothiazine and undergoes no more transformations. C- $\alpha$  also remains attached to nitrogen when the side chain breakdown is induced by sulfuric acid. Lagercrantz<sup>124</sup> noted that when promethazine and aprobit are dissolved in H<sub>2</sub>SO<sub>4</sub> abundant foaming occurs and the ESR spectra of the solutions thus obtained show a quadruplet. The same spectra are given by D<sub>2</sub>SO<sub>4</sub> solutions; if 146 underwent C—N splitting, the ESR spectrum in D<sub>2</sub>SO<sub>4</sub> would show a triplet, as obtained from solutions of unsubstituted phenothiazine in the same solvent. The structure of the group attached to nitrogen in 146 formed in sulfuric acid is not elucidated. Lagercrantz assumed that it is a —CH<sub>2</sub>OH

<sup>389</sup> T. Waaler, *Pharm. Acta Helv.* **35**, 168 (1960).

group in a fixed configuration so that only one proton can interact with the odd electron responsible for the ESR signal. Since similar signals are obtained from promethazine and aprobit adsorbed on Dowex 50 activated with  $\text{Fe}^{3+}$ , it is concluded that the resin also causes fission of the side chain.<sup>124</sup>



SCHEME 17

Ammonium persulfate can induce a more complete degradation of *N*-substituted phenothiazines. A systematic study of this reaction led Nano and co-workers<sup>390-392</sup> to conclude that an amine, two aldehydes, and colored phenothiazine derivatives are the final products when there are two carbon atoms in the side chain. This means that both **146** and **147** are *C*-oxygenated, very probably hydroxylated<sup>124, 392</sup>; **149** and **150** are aldehydes, and **148** represents a mixture of quinonoid compounds, the most important being phenothiazone. The formation of the latter upon oxidative degradation of 10-[2,3-bis(dimethylamino)propyl]phenothiazine with  $\text{KClO}_3$  in  $\text{H}_3\text{PO}_4$  has also been observed.<sup>393</sup>

<sup>390</sup> G. M. Nano, *Congr. Sci. Farm., 21st Conf. Commun., Pisa, 1961* p. 741. Federazione Ordini Farm. Ital., Rome, 1962.

<sup>391</sup> G. M. Nano and P. Sancin, *Atti Accad. Sci. Torino: Classe Sci. Fis., Mat. Nat.* **95**, 187 (1961); *Chem. Abstr.* **61**, 3102a (1964).

<sup>392</sup> G. M. Nano, P. Sancin, and G. Tappi, *Pharm. Acta Helv.* **38**, 623 (1963).

<sup>393</sup> L. Vignoli, F. Gouezo, and J. Guillot, *Bull. Soc. Pharm. Marseille* **13**, 55 (1964).

*b. Three Carbon Atoms.* When there are three carbon atoms separating the two nitrogen atoms, as with the psychoactive phenothiazine drugs, transient colorations are formed with ammonium persulfate, the final product of the reaction being the colorless 5-oxide with the side chain retained. The presence of a substituent, e.g., chlorine or methoxyl, in position 2 of the ring exerts little influence upon sulfoxide formation.

The first stage of oxidation is the removal of an electron, a colored cation radical being formed, which carries a partial positive charge on the nitrogen at position 10. The nitrogen atom in the side chain is usually also positively charged, since most of the phenothiazine drugs are salts. The further course of the reaction is determined by the interaction between the two positive centers exerted through the chain of carbon atoms and inducing a positive charge on the carbon atom adjacent to the heterocyclic nitrogen (cf. Section IV, D). This charge is smaller, the longer the side chain; thus the stability of the three-carbon side chains is explained. The importance of these considerations to the metabolism of phenothiazine drugs is obvious.

Decomposition which probably involves the fission of a 10-substituent with a three-carbon chain has however been observed upon photochemical oxidation of drugs.<sup>238, 394, 395</sup>

In connection with the stability of aqueous solutions of phenothiazine drugs, it has been suggested that simple probability theory could be used to determine the composition of the ionic environment around a drug molecule, and to predict thereby the stability of various salts of the same drug.<sup>396</sup>

## B. OXYGENATED FUNCTIONS

### 1. *Hydroxy Derivatives*

As far as ring hydroxy groups are concerned, the conversion into esters and ethers has been carried out only on 3-hydroxyphenothiazines, readily available from phenothiazones. Thus, 3-acetoxyphenothiazine was prepared on acetylating 3-hydroxyphenothiazine with acetic anhydride.<sup>81</sup>

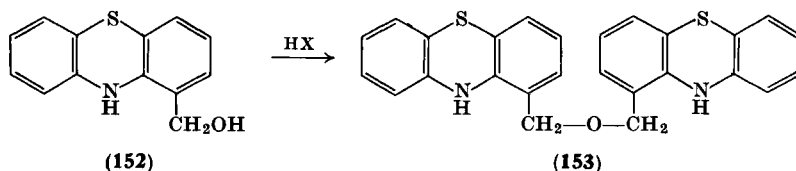
<sup>394</sup> E. Pawelczyk and T. Dopierala, *Farm. Polska* **18**, 234 (1962); *Chem. Abstr.* **58**, 1303g (1963).

<sup>395</sup> J. Floderer and V. Horvathy, *Acta Pharm. Hung.* **35**, 98 (1965); *Chem. Abstr.* **63**, 16160c (1965).

<sup>396</sup> L. Kennon and Kuo-Sin Chen, *J. Pharm. Sci.* **51**, 1149 (1962).

Bodea and Fărcășan prepared acetoxy, benzyloxy, and methoxy derivatives from tri- and tetrachloro-3-hydroxyphenothiazine.<sup>217</sup> Reduction of phenothiazine followed by a treatment with dimethyl sulfate led to 3-methoxyphenothiazine.<sup>218</sup> The synthesis of some *O*-glucosides from halogenated 3-hydroxyphenothiazines has been performed recently.<sup>397</sup>

Treatment of methoxy derivatives with pyridine hydrochloride gave hydroxyphenothiazines. This reaction was applied to 1-, 2-, and 3-methoxyphenothiazine.<sup>379</sup> Benzyloxy groups in position 2 readily undergo reductive cleavage with sodium in isoamyl alcohol;



consequently, benzyl residues have been recommended as protecting groups for hydroxyls in the thionation reactions.<sup>398</sup> Loss of 2-benzyloxy groups takes place when *N*-alkylation is carried out using sodamide as condensing agent.<sup>399</sup>

The ether **153** was the result of attempts to convert 1-hydroxymethylphenothiazine (**152**) into the corresponding halomethyl derivatives by means of halogen acids.<sup>299</sup>

## 2. Aldehydes and Ketones

Condensation reactions have been carried out with aldehydes in positions 2 and 3.

Some 3-formyl-10-alkylphenothiazines with substituted phenylhydrazines gave phenylhydrazones (**154**) which on boiling with sodamide in xylene yielded *N*-aryl amidines (**155**).

<sup>397</sup> C. Bodea, V. Fărcășan, and T. Panea, *Rev. Roumaine Chim.* **12**, 697 (1967).

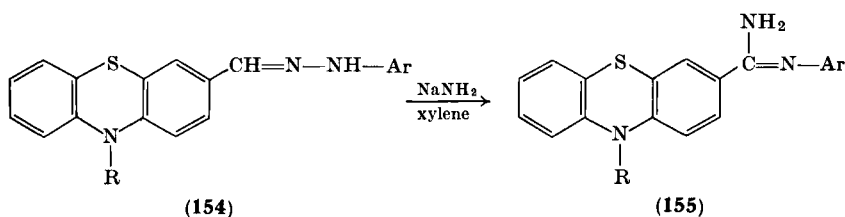
<sup>398</sup> Chao Ho Ts'ao, Chia Yu Hu, Kuei-Shen Lu, To-Kai Cheng, Chih-Chung Chao, and Hsiao Tien Liang, *Yao Hsueh Hsueh Pao*, **10**, 394 (1963); *Chem. Abstr.* **59**, 13971g (1963).

<sup>399</sup> P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. M. Pavloff, and Ch. L. Zirkle, *J. Org. Chem.* **25**, 944 (1960).

The structure of the amidines was proved by hydrolysis to aniline and by their conversion into 10-methylphenothiazine-3-carboxylic acid.<sup>400</sup>

Rhodanines have been obtained from 3-formyl-10-methylphenothiazine<sup>401</sup> and its 5,5-dioxide.<sup>60</sup> From these two aldehydes and also from 2-formyl- and 2-formyl-10-methylphenothiazine, azlactones have been prepared,<sup>60</sup> and their physical properties and oxazolone ring-opening reactions have been investigated.<sup>402</sup>

Wolff-Kishner reduction of aldehydes to methyl groups has been performed in some structure proofs.<sup>332, 345</sup>



Conversion of some 3-formyl-10-alkylphenothiazines to the corresponding carboxylic acids has been carried out with either alkaline hydroxides or silver oxide.<sup>403</sup> Oxidation of the aldehyde to carboxyl concomitantly with oxidation at the sulfur bridge to the 5,5-dioxide can be effected with alkaline  $\text{KMnO}_4$ .<sup>60</sup>

Most of the reactions of the phenothiazinyl ketones discussed here were carried out on compounds of the 2 series readily available by Friedel-Crafts acylation (See Section V, A, 4, c); many products derived from these ketones are of pharmacological importance.

For characterization of the ketones, oximes have been used<sup>86, 330</sup>; 2-acetylphenothiazine with hydroxylamine on an ion-exchange column was claimed to be an efficient procedure.<sup>404</sup>

<sup>400</sup> S. Robev and N. Panov, *Compt. Rend. Acad. Bulgare Sci.* **17**, 577 (1964); *Chem. Abstr.* **62**, 6479b (1965).

<sup>401</sup> A. Mackie and A. L. Misra, *J. Chem. Soc.*, 3919 (1954).

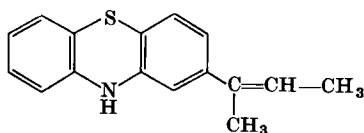
<sup>402</sup> C. Bodea, V. Fărcășan, and I. Oprean, *Rev. Roumaine Chim.* (1967) (in press).

<sup>403</sup> G. Cauquil, A. Casadevall, and E. Casadevall, *Compt. Rend.* **240**, 1997 (1955).

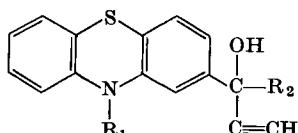
<sup>404</sup> S. Dokic and M. Cakara, *Kem. Ind. (Zagreb)* **13**, 261 (1964); *Chem. Abstr.* **61**, 10545c (1964).



A comprehensive comparative survey of the Schmidt reaction and the Beckmann rearrangement of acetyl- and benzoylphenothiazines into aminophenothiazines has been reported by Cauquil *et al.*<sup>303</sup> The Schmidt reaction yielded the desired intermediate amides (i.e., the acyl derivatives of the aminophenothiazines). Beckmann rearrangement of the oximes, however, led to acylaminophenothiazines only when starting with *C*-acetylphenothiazines; the corresponding benzoyl derivatives yielded the anilides of phenothiazine carboxylic acids, the products resulting from migration of the phenyl rather than the bulkier phenothiazinyl group. This is a somewhat unexpected result, although several analogies may be found in the literature.



(156)



(157)

Since 2-acetylphenothiazine undergoes an autocondensation with sodamide, the introduction of a substituent in position 10 using this base as condensing agent requires protection of the keto group. This may be achieved by ketalization with ethylene glycol or by conversion into Schiff bases; derivatives stable in alkaline medium are thus obtained, from which the ketones may be liberated by acidification after *N*-alkylation.<sup>374</sup>

The reaction of 2-acetylphenothiazine with ethyl magnesium bromide led to 2-(but-2-enyl)phenothiazine (156)<sup>374</sup>; *N*-substituted ketones gave ethynyl derivatives (157) on treatment with acetylene.<sup>92</sup>

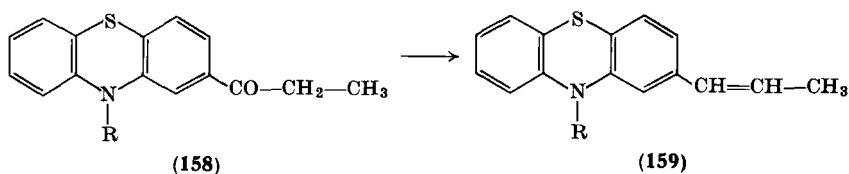
Reduction of 2-acyl derivatives to alcohols has been performed by the Meerwein-Ponndorf reaction and by using  $\text{LiAlH}_4$ .<sup>90, 91, 150</sup> Polarographic one-electron reduction of the keto group in 10-acetyl-2-( $\beta$ -piperidinopropionyl)phenothiazine has been reported.<sup>405</sup>

The Leuckhardt reaction has been applied to 2-acetylphenothiazine, giving 1-(2-phenothiazinyl)ethylamine.<sup>90</sup>

Wolff-Kishner reduction of 2-acylphenothiazines, also used in earlier works, was extended to a series of new compounds.<sup>67, 85-87, 90, 91, 298, 337</sup> Reduction of 2-propionyl- (158) and 2-butyrylphenothia-

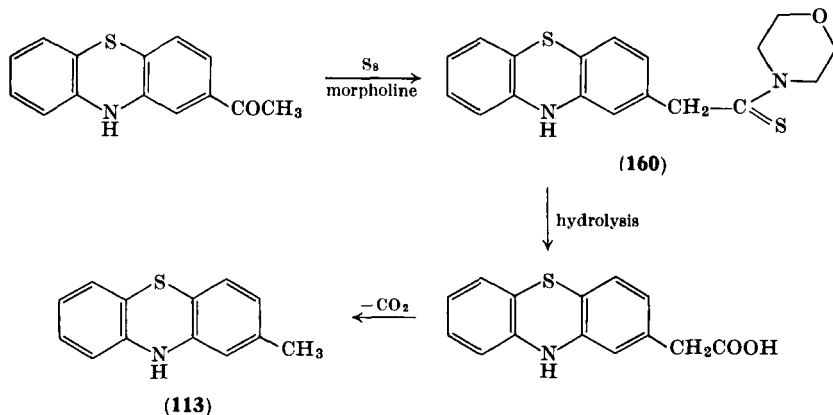
<sup>405</sup> M. Sterescu, N. Keim, and M. Popa, *Rev. Chim. (Bucharest)* **11**, 487 (1960); *Chem. Abstr.* **58**, 240c (1963).

zine under Clemmensen conditions gives good yields of 2-alkenyl derivatives (**159**).<sup>67</sup> It is of interest that the reaction does not proceed through the carbinol, as shown by the fact that the carbinol remains unchanged under the conditions of the Clemmensen reaction.



Borohydride reduction of ketones to carbinols, and their (normal) Clemmensen reduction, has also been carried out.<sup>91</sup>

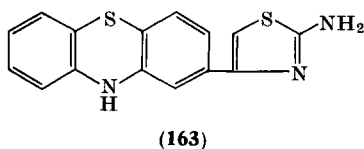
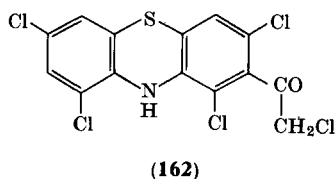
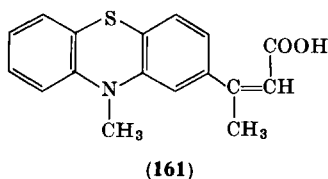
Burger and Clements<sup>298</sup> converted 2-acetylphenothiazine into  $\alpha$ -(2-phenothiazinyl)thioacetomorpholide (**160**) with sulfur and morpholine in a Willgerdt reaction; hydrolysis of the latter to  $\alpha$ -(2-phenothiazinyl)acetic acid, which on decarboxylation gave 2-methylphenothiazine (**113**), was reported by Massie *et al.*<sup>90</sup> The same reaction sequence has been performed recently starting from 2-chloro-8-acetylphenothiazine.<sup>339</sup>



Condensation of 2-acetyl-10-methylphenothiazine with acetic anhydride gives the product **161**.<sup>332</sup>

Reactions at the active  $\alpha$ -methyl or  $\alpha$ -methylene group have also been investigated. Under Mannich reaction conditions 10-methylphenothiazinyl 2- and 3-ketones yielded the expected products.<sup>91</sup>

Fujimoto<sup>295</sup> chlorinated 2-acetylphenothiazine and obtained a product to which structure **162** was assigned. One of the chlorine atoms is very labile, in agreement with the observation of Massie *et al.*<sup>90</sup> that in 2-chloroacetylphenothiazine the chlorine may easily be replaced by Br, I, CN, and thiourea; the latter yields 2-amino-4-(2-phenothiazinyl)thiazole (**163**).



Kröhnke-King oxidative degradation of acetyl and chloroacetyl groups at various positions led to carboxylic acids.<sup>298, 335, 349, 350</sup> The haloform oxidation with hypochlorite convert acetyl groups at positions 1 and 2 into carboxylic acids and also oxidizes to the 5,5-dioxide.<sup>331, 332, 335, 349, 350</sup> Working in heterogeneous phase, acids unoxidized at sulfur may be obtained. The same results are obtained on oxidation under alkaline conditions.<sup>332</sup> Oxidation of acetyl to carboxyl groups with  $\text{KMnO}_4$  is also mentioned in the literature.<sup>330</sup>

### 3. Carboxylic Acids and Their Derivatives

The availability of phenothiazine carboxylic acids makes them very convenient starting materials for the preparation of other derivatives.

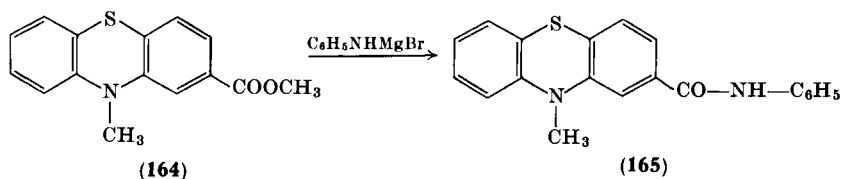
To obtain compounds with potential pharmacological activity, and for characterization, carboxylic groups have been converted into esters and hydrazides.<sup>331, 339, 349, 350, 385, 403, 406</sup>

The methyl ester of 10-methylphenothiazine-4-carboxylic acid was converted into the 4-hydroxymethyl derivative on reaction with  $\text{LiAlH}_4$ ; the product was identical to that obtained on metalation

<sup>406</sup> J. de Antoni, *Bull. Soc. Chim. France*, 2214 (1964).

of 10-methylphenothiazine followed by treatment with formaldehyde.<sup>349, 350</sup> A similar reduction has been carried out on phenothiazine-1-carboxylic acid.<sup>299</sup>

Of particular importance is the conversion of phenothiazine-2-carboxylic acids into aldehydes, because this is the only route to 2-formylphenothiazine so far reported.<sup>331, 332</sup> McFadyen-Stevens reduction was utilized and the same method was applied to prepare 3-formyl-10-methylphenothiazine-5,5-dioxide.<sup>60</sup>



The acid chloride of phenothiazine-1-carboxylic acid has been prepared by treating the acid with the calculated amount of  $\text{PCl}_5$  in benzene,<sup>153</sup> thus avoiding ring chlorination<sup>153, 297, 298</sup> (see Section V, A, 1, d). Another way to prevent ring chlorination in this reaction is first to acylate at position 10.<sup>406</sup> Some amides have been prepared from phenothiazine carboxylic acid chlorides<sup>91, 303</sup> and Curtius degradations performed.<sup>303</sup>

Attempts to apply the Curtius reaction to phenothiazine-1-carboxylic acid yielded a very hydrolysis-resistant pyrazolone.<sup>153, 297</sup>

$\text{LiAlH}_4$  reduction of amides to the aminomethylphenothiazines has been reported.<sup>91, 407</sup> A procedure for obtaining long-chain aliphatic aldehydes has been developed using the action of  $\text{LiAlH}_4$  upon the amides obtained from carboxylic chlorides and phenothiazine (in position 10). Very good yields were thus obtained.<sup>408</sup>

The magnesium amide prepared from ethyl magnesium bromide and aniline, with 2-carbomethoxy-10-methylphenothiazine (164), gives the anilide 165.

Carboxyl groups at position 2 have been converted into nitriles via the amides.<sup>298</sup> 2-Cyanophenothiazine was also obtained from 2-chlorophenothiazine and  $\text{CuCN}$ .<sup>353, 354</sup> The action of  $\text{H}_2\text{S}$  upon

<sup>407</sup> V. A. Skorodumov, E. N. Il'chenko, and S. V. Zhuravlev, *Zh. Obshch. Khim.* **30**, 3095 (1960); *Chem. Abstr.* **55**, 21128h (1961).

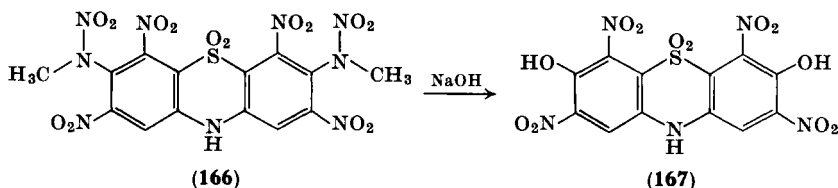
<sup>408</sup> H. Kaufmann and H. Kirschnek, *Fette, Seifen, Anstrichmittel* **55**, 851 (1953).

2-cyanophenothiazine gave the thioamide.<sup>409, 410</sup> Grignard reagents have been used to convert some cyanophenothiazines into carbonyl derivatives; 3-benzoyl-10-methylphenothiazine thus prepared was identical to that obtained on Friedel-Crafts acylation of 10-methylphenothiazine.<sup>335</sup> (see, however, Section V, A, 4, c).

## C. NITROGEN-CONTAINING FUNCTIONAL GROUPS

### 1. *Amines*

All aminophenothiazines, and especially 3-amino and 3,7-diamino derivatives, are very sensitive to oxygen. Substitution in position 10 and oxidation at the level of the sulfur bridge increase the stability.



A series of acyl derivatives of the amines at various positions have been prepared, including benzoyl derivatives,<sup>303</sup> carbonates,<sup>64, 411</sup> and acyl derivatives with *N*-acylated amino acid<sup>61</sup> and with  $\omega$ -chlorocarboxylic acid residues.<sup>73, 407</sup> The latter have been reduced with  $\text{LiAlH}_4$  to the corresponding alkylamino derivatives.<sup>407</sup>

Continuing the work of Gnehm<sup>412</sup> on the nitration of methylene blue, Urbański *et al.*<sup>314, 315</sup> obtained a higher nitrated product, to which structure **166** was assigned; in both dimethylamino groups, one of the methyls has been replaced by a nitro group. Hydrolysis to the phenolic compound (**167**) was taken as evidence for the proposed structure. If this is correct, Gnehm's nitration product, which is an intermediate in the formation of **166**, must also have an *N*-methylnitramine structure.

<sup>409</sup> Société des Usines Chimiques Rhône-Poulenc, Belgian Patent 612,885; *Chem. Abstr.* **58**, 1470h (1963).

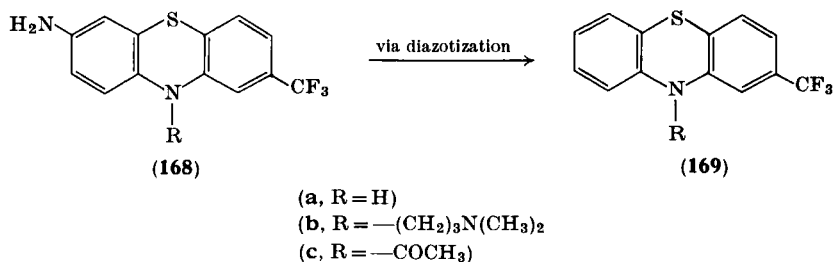
<sup>410</sup> Rhône-Poulenc S.A., French Patent (M) 1647; *Chem. Abstr.* **59**, 2829d (1963).

<sup>411</sup> A. N. Gritsenko and S. V. Zhuravlev, *Zh. Obshch. Khim.* **33**, 3697 (1963); *Chem. Abstr.* **60**, 8024c (1964).

<sup>412</sup> R. Gnehm, *J. Prakt. Chem.* **76**, 407 (1907).

Schiff bases have been prepared from 3-amino-10-alkylphenothiazine and 3-amino-10-alkyl-phenothiazine-5,5-dioxides, and from 2-aminophenothiazine, to characterize the amines and to obtain potentially useful compounds.<sup>61, 73, 413, 414</sup>

Diazotization of aminophenothiazines yields the expected results only when there is stabilization of the amino groups by suitable ring substituents. 3-Amino-10-methylphenothiazine and 3-amino-10-ethylphenothiazine-5,5-dioxide have been diazotized and coupled with hydroxy- and aminonaphthalenes.<sup>61, 415</sup> Diazo groups have only been successfully replaced by hydrogen and chlorine. Thus, Flory



and Restivo<sup>416</sup> diazotized 2-trifluoromethyl-7-aminophenothiazine (168a) and the 10-dimethylaminopropyl derivative of the latter (168b) and, by refluxing the solutions of the diazo derivatives with alkaline isopropanol, replaced the diazo groups by hydrogen. Better results were obtained with 7-amino-2-trifluoromethyl-10-acetylphenothiazine (168c).<sup>417</sup>

For structural confirmation of some chlorophenothiazines, and to other ends, some diazo derivatives were converted into chloro compounds by the Sandmeyer reaction.<sup>252-254, 259, 289, 317, 319, 416</sup>

<sup>413</sup> D. Simov and E. M. Simova, *Compt. Rend. Acad. Bulgare Sci.* **11**, 407 (1958); *Chem. Abstr.* **53**, 18045g (1959).

<sup>414</sup> S. V. Zhuravlev and V. A. Skorodumov, *Zh. Organ. Khim.* **1**, 363 (1965); *Chem. Abstr.* **62**, 16236a (1965).

<sup>415</sup> E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *J. Med. Chem.* **6**, 646 (1963).

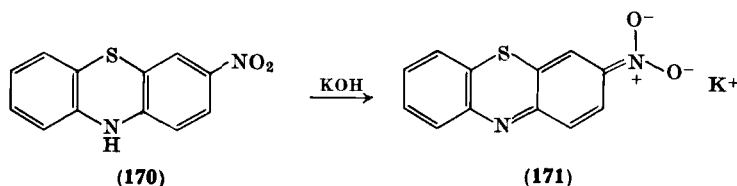
<sup>416</sup> K. G. Flory and A. R. Restivo, *J. Org. Chem.* **23**, 1018 (1958).

<sup>417</sup> J. Schwartz (Olin Mathieson Chemical Corp.), U.S. Patent 2,997,468; *Chem. Abstr.* **56**, 1460d (1962).

Acylated 2- and 3-aminophenothiazines have been hydrolyzed.<sup>411, 418, 419</sup> Since direct alkylation of aminophenothiazines fails,<sup>407</sup> the conversion of acylaminophenothiazines into the corresponding alkylamino derivatives using  $\text{LiAlH}_4$ <sup>91, 407</sup> is of preparative interest.

## 2. Nitro Derivatives

Reduction of nitrophenothiazines to amines has been carried out under various conditions. Sn and HCl,<sup>247, 252, 259, 316, 317</sup>  $\text{SnCl}_2$ ,<sup>253, 319</sup> Zn and acetic acid,<sup>287</sup> and Fe with HCl or aqueous ethanol- $\text{CaCl}_2$ <sup>313, 416, 417</sup> have been used. Hydrogen and Raney nickel under



mild conditions reduced nitro derivatives to amines without desulfurization; hydrazine hydrate and Raney nickel in methanol selectively reduced 3-nitro-10-methylphenothiazine-5-oxide to the corresponding 3-amino derivative without affecting the sulfoxide oxygen.<sup>64</sup> Hydrogenation in the presence of platinum has also been used.<sup>299</sup>

Working in the presence of acetic anhydride, acylating reduction of several 2-nitrophenothiazines was carried out; it is assumed that both acetyl groups in the diacetyl derivative thus obtained are located at the exocyclic nitrogen.<sup>74</sup>

*N*-Unsubstituted 3-nitro- (170), and 3,7-dinitrophenothiazines yield blue products with alkalis,<sup>327</sup> probably salts.<sup>299</sup>

The intense blue colors obtained upon treatment of 3-nitrophenothiazines with alcoholic KOH distinguish them from 2-nitrophenothiazines, which give red-violet colors.<sup>74</sup>

Toei<sup>309, 311</sup> recommended a procedure for the gravimetric assay of  $\text{K}^+$ , using 1,3,7,9-tetranitrophenothiazine-5-oxide or -5,5-dioxide in  $\text{LiOH}$  or  $\text{Li}_2\text{CO}_3$  solution as a precipitating reagent.

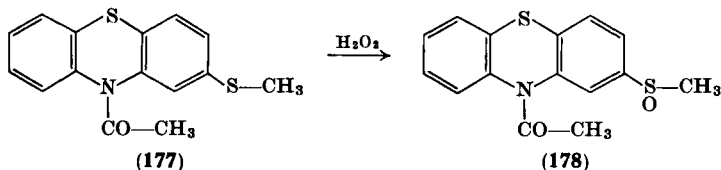
<sup>418</sup> S. V. Zhuravlev and V. A. Skorodumov, *Zh. Obshch. Khim.* **31**, 3129 (1961); *Chem. Abstr.* **56**, 15504c (1962).

<sup>419</sup> A. A. Cherkasova and S. V. Zhuravlev, *Zh. Obshch. Khim.* **33**, 2315 (1963); *Chem. Abstr.* **59**, 13973h (1963).

<sup>422</sup> Rhône-Poulenc S.A., Belgian Patent 612,886; *Chem. Abstr.* **59**, 1653b (1964).



Selective oxidation ( $\text{H}_2\text{O}_2$ ) of 2-methylthio-10-acetylphenothiazine (177) yielded the 2-methylsulfinyl derivative (178), the acetyl at position 10 protecting the ring sulfur from oxidation.<sup>423</sup>



## VII. Oxidations and Reductions at the Sulfide Bridge

Phenothiazine and most of its derivatives readily undergo various oxidative transformations, depending upon the reagent, conditions, and ring substituents. The reactions yielding free radicals, phenazathionium salts, and ring oxygenated derivatives, by chemical and electrochemical methods, have been discussed in Section IV. The reactions which lead to 5-oxides without the intermediacy of the phenazathionium cation, and to 5,5-dioxides, and the reductions of 5-oxides to the corresponding phenothiazines, are reviewed in this section.

No preparative reduction of a phenothiazine-5,5-dioxide has so far been reported.

### A. OXIDATION TO 5-OXIDES AND 5,5-DIOXIDES

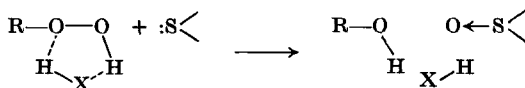
Although many early reports of oxidation of phenothiazines to 5-oxides and 5,5-dioxides may be found, efficient preparative methods for these compounds have been elaborated only in recent years. Oxidation at the sulfur bridge improves the stability of some ring-substituted derivatives (e.g., amines, Section VI, C, 1). Such oxidations often accompany ring substitution (e.g., nitration, see Section V, A, 2) or reactions involving functional groups on the ring (e.g., haloform oxidation of C-acetylphenothiazines, see Section VI, B, 2).

#### 1. Unsubstituted 5-Oxide and 5,5-Dioxide

Particular difficulties were encountered in the preparation of unsubstituted phenothiazine-5-oxide and phenothiazine-5,5-dioxide,

<sup>423</sup> J. Renz, J. P. Bourquin, and G. Schwarb (Sandoz Ltd.), U.S. Patent 3,084,161; *Chem. Abstr.* **59**, 10072a (1963).

because side reactions readily occur. Bodea *et al.*<sup>424, 425</sup> developed two procedures for preparing phenothiazine-5-oxide; these methods are also applicable to some lower substituted derivatives. The first<sup>424</sup> makes use of alkyl hydroperoxides as oxidizing agents; almost quantitative yields were obtained with tetrahydrofuran and dioxan enriched in peroxides by autoxidation. Moreover, the ease with which phenothiazine reacts with peroxides suggested a procedure for



SCHEME 18

removing peroxides from ethers.<sup>426</sup> The formation of sulfoxides under these conditions involves an electrophilic attack of the peroxide oxygen at the phenothiazine sulfur (Scheme 18<sup>427</sup>), and not by a nucleophilic mechanism involving the phenazathionium cation.

The second method of preparation is the oxidation with nitric acid in acetic acid of the readily available 10-benzoylphenothiazine, which proceeds very selectively and yields only 10-benzoylphenothiazine-5-oxide. Alkaline hydrolysis then gives phenothiazine-5-oxide in 85% overall yield.<sup>425</sup>

10-Acetyl<sup>311</sup> and 10-benzoyl<sup>310</sup> groups have been used for protection in the preparation of phenothiazine-5,5-dioxide by  $\text{H}_2\text{O}_2$  oxidation.

## 2. 5-Oxides of Substituted Phenothiazine

Atmospheric oxygen may oxidize phenothiazine and some of its *N*-substituted derivatives; this is of importance in connection with the antioxidant action of phenothiazine, a substance widely used in preventing lubricant autoxidation. On bubbling air through a solution of an autoxidizable substance to which phenothiazines are added, the latter are converted into oxidized products, as far as the phenothiazones, with phenothiazine-5-oxides as intermediates. The 5-oxide

<sup>424</sup> C. Bodea and I. Silberg, *Studii Cercetari Chim. (Cluj)* **14**, 317 (1963); *Chem. Abstr.* **62**, 14664h (1965).

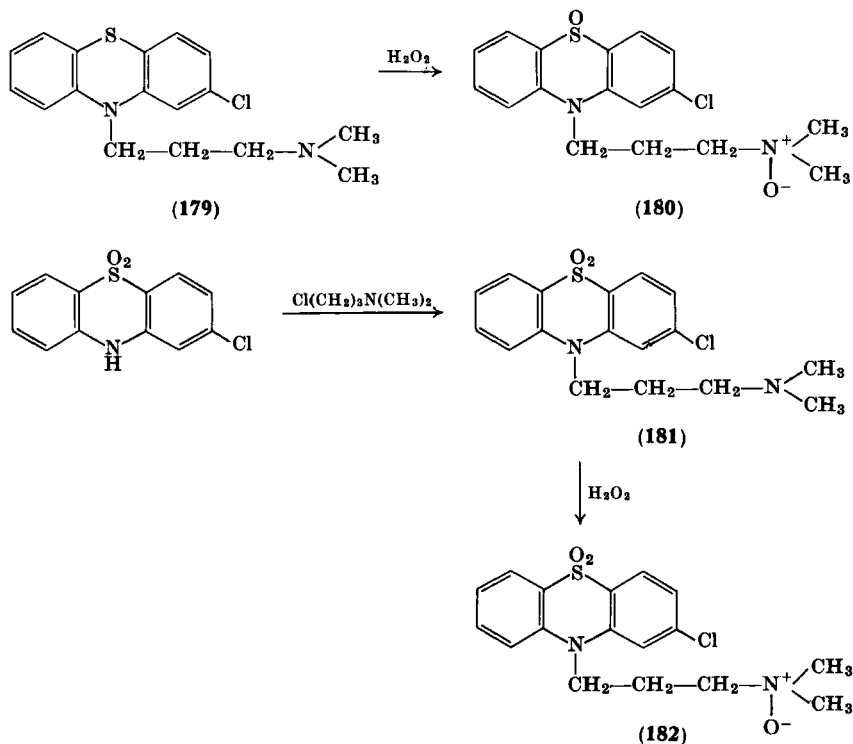
<sup>425</sup> C. Bodea and M. Răileanu, *Studii Cercetari Chim. (Cluj)* **11**, 129 (1960); *Chem. Abstr.* **55**, 7422e (1961).

<sup>426</sup> C. Bodea and I. Silberg (Ministerul Industriei Petrolului și Chimiei, Romania), Belgian Patent 625,714 and German Patent 1,216,279; *Chem. Abstr.* **59**, 10066f (1963).

<sup>427</sup> K. U. Ingold, *Chem. Rev.* **61**, 563 (1961).

was actually isolated from 10-methylphenothiazine<sup>427</sup>; in other cases the reaction kinetics suggest its intermediacy.<sup>428</sup> The capacity of phenothiazine to react with hydroperoxides is largely responsible for its antioxidant action. Adsorbed phenothiazines are readily converted into 5-oxides by atmospheric oxygen, which has been used for analytical purposes.<sup>429, 430</sup>

Photooxidation to 5-oxides was noticed when aqueous solutions of some phenothiazine drugs were exposed to light.<sup>231, 232, 238, 431</sup>



SCHEME 19

<sup>428</sup> T. Colclough and J. I. Cunneen, *J. Chem. Soc.*, 4790 (1964).

<sup>429</sup> C. Korczak-Fabierkiewicz, J. Kofoed, and G. H. W. Lucas, *J. Forensic Sci.* **10**, 308 (1965).

<sup>430</sup> J. Kofoed, C. Korczak-Fabierkiewicz, and G. H. W. Lucas, *Nature* **211**, 147 (1966).

<sup>431</sup> S. Fujisawa and S. Kawabata, *Yakugaku Zasshi* **86**, 510 (1966); *Chem. Abstr.* **65**, 10585d (1966).

Ozone oxidizes phenothiazine and some of its substituted derivatives to 5-oxides.<sup>432</sup> Selective oxidation of *N*-alkylphenothiazines to 5-oxides is conveniently performed by means of sodium nitrite in acetic acid.<sup>254, 317, 320</sup> In some cases, for example that of 3,7-dinitrophenothiazine<sup>310</sup> and octachlorophenothiazine,<sup>79</sup> nitric acid may be used as a selective oxidant for obtaining pure 5-oxides. Chlorine oxidizes octachlorophenothiazine in nitrobenzene in the presence of water to the corresponding 5-oxide.<sup>237</sup> Almost quantitative yields of 5-oxides have been reported in the oxidation of *N*-methylphenothiazine, and of 10-dialkylaminoalkylphenothiazines in which there are three carbon atoms in the side chain, with ammonium persulfate<sup>390-392</sup> (see also Section VI, A). Some halo- and halonitrophenothiazines may be converted into 5-oxides by dichromate.<sup>210, 216, 236</sup>

Using the calculated amount of hydrogen peroxide the 5-oxides of many phenothiazine drugs have been prepared.<sup>69, 78</sup> Chlorpromazine (179) yields the *N*-oxide of the 5-oxide (180) without oxidation at sulfur to the 5,5-dioxide. Chlorpromazine-5,5-dioxide (181) was prepared indirectly, as shown in Scheme 19; it may be further oxidized to the *N*-oxide (182).<sup>433</sup> *m*-Chloroperbenzoic acid oxidation has been used with 2-trifluoromethylphenothiazine-1-carboxylic acid.<sup>352</sup>

### 3. 5,5-Dioxides of Substituted Phenothiazines

In many cases, 5,5-dioxides have been obtained using the same reagents as for the 5-oxides, by prolonging the reaction time. Hydrogen peroxide appears to be the most convenient oxidant (see, for example, references 22, 77, 78, 99, 216, 236, 237, 244, 247, 252, 254, 255, 259, 287, 310, 319, 320, 352, 434, 435).

It has recently been found that nitric acid, which usually oxidizes the phenothiazines only to 5-oxides, may lead in some cases to the dioxides.<sup>79, 312, 314, 315</sup>

Sodium hypochlorite has been used to oxidize 10-alkylphenothiazine-3-carboxylic acids to the 5,5-dioxides.<sup>403</sup> Potassium permanganate also yields dioxides.<sup>60, 317</sup>

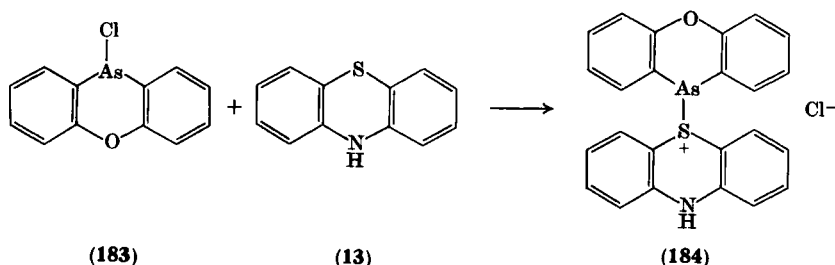
<sup>432</sup> M. Nakanishi and N. Kuriyama (Yoshitomi Pharmaceutical Co.), Japanese Patent 15,617 (1961); *Chem. Abstr.* **56**, 12908i (1962).

<sup>433</sup> H. Kanô and M. Fujimoto, *Pharm. Bull. (Tokyo)* **5**, 389 (1957).

<sup>434</sup> D. Simov and N. Mitrovska, *Compt. Rend. Acad. Bulgare Sci.* **11**, 485 (1958); *Chem. Abstr.* **54**, 1526e (1960).

<sup>435</sup> H. Wunderlich and A. Stark, *Pharmazie* **20**, 519 (1965).

A special case of oxidation at the sulfide bridge is in the preparation of the sulfonium salt **184** starting with **183**.<sup>436</sup>



### B. REDUCTION OF 5-OXIDES

Phenothiazine-5-oxides may be reduced by a variety of photochemical, electrochemical, and chemical methods. The only case of 5,5-dioxide reduction reported is the polarographic reduction.<sup>437</sup>

Fujisawa and co-workers<sup>231, 232, 238, 421</sup> reported photochemical reduction of some phenothiazine drug 5-oxides, when the latter were irradiated with white fluorescent light in aqueous solution under nitrogen. Reducing agents like ascorbic acid and sulfite have an accelerating action upon the reductive process, whereas maleic and picolinic acids inhibit it.

Phenothiazine estimation may be carried out by oxidation with diluted nitric acid followed by polarographic reduction. The polarographic waves at  $-0.68$  V thus obtained have been assigned to the reduction of the 5-oxide.<sup>438</sup>

A series of 5-oxides of phenothiazines and benzophenothiazines, some of which were *N*-acetylated, have been polarographically reduced in ethanolic solution; they displayed behavior similar to that of other aromatic *S*-oxides. The reduction proceeds more easily in acid media, because at lower pH phenothiazine-5-oxides are in equilibrium with the corresponding phenazathionium salts, which undergo a one-electron reduction (see Section IV, B, 1). The cation radical thus formed cannot be further reduced under these condi-

<sup>436</sup> S. J. Strycker (Dow Chemical Co.), U.S. Patent 3,117,123; *Chem. Abstr.* **61**, 667c (1964).

<sup>437</sup> N. A. Kudryavtseva, Z. V. Pushkareva, and V. F. Gryazev, *Zh. Obshch. Khim.* **35**, 14 (1965); *Chem. Abstr.* **62**, 13024b (1965).

<sup>438</sup> S. Usami, *Bunseki Kagaku* **10**, 626 (1961); *Chem. Abstr.* **56**, 443b (1962).

tions.<sup>437</sup> Polarographic reduction of the sulfoxides derived from a series of phenothiazine drugs has been reported.<sup>154</sup>

Raney nickel has been suggested for preparing some phenothiazine drugs from their 5-oxides.<sup>439, 440</sup> Stannous chloride successfully reduces some 5-oxides.<sup>244, 300, 441</sup>

The removal of the sulfoxide oxygen by halogen acids is accompanied in the case of HCl and HBr by ring halogenation (Section IV, G, 4). With hydriodic and hydrofluoric acids only reduced products without ring substitution were isolated.<sup>246, 442</sup>

Triphenylsilyllithium and diphenylsilane reduced 10-ethyl-phenothiazine-5-oxide to 10-ethylphenothiazine.<sup>443</sup>

### VIII. Metabolism of Phenothiazines

The great amount of research on the mode of action and the metabolism of phenothiazine derivatives is a natural result of their application in human and veterinary medicine. In the early years (1935–1940) the main object of investigation was the metabolism of phenothiazine, its 5-oxide, and some of their *C*-substituted derivatives in animal organisms, arising out of the anthelmintic action of these substances. During the postwar period, comparatively little attention was paid to these topics; recent research has confirmed the principal conclusions of the earlier work, namely that the main metabolic pathway followed by simple phenothiazines is the oxidation to the 5-oxide and hydroxylation in positions 3 and 7.<sup>444–448</sup> After the

<sup>439</sup> M. Izumi, M. Sumita, M. Nakanishi, and T. Nishino (Yoshitomi Pharmaceutical Industries, Ltd.), Japanese Patent 2678 (1957); *Chem. Abstr.* **52**, 4698a (1958).

<sup>440</sup> M. Nakanishi (Yoshitomi Drug Manufg. Co.), Japanese Patent 925 (1960); *Chem. Abstr.* **54**, 19725h (1960).

<sup>441</sup> K. Morisawa, Y. Terai, S. Kawahara, K. Ichikawa, and Y. Oka, *Yakugaku Kenkyu* **29**, 161 (1957); *Chem. Abstr.* **53**, 8145e (1959).

<sup>442</sup> M. Tsunoda and T. Nishino (Yoshitomi Drug Mfg. Co.), Japanese Patent 16439 (1960); *Chem. Abstr.* **56**, 5977a (1962).

<sup>443</sup> J. W. Diehl and H. Gilman, *Chem. & Ind. (London)*, 1095 (1959).

<sup>444</sup> T. Ellison and A. C. Todd, *Am. J. Vet. Res.* **18**, 519 (1957).

<sup>445</sup> F. Alexander, A. Mackie, N. Ghatge, and A. W. Waddell, *Arch. Intern. Pharmacodyn.* **113**, 254 (1958).

<sup>446</sup> T. Richardson and A. C. Todd, *Am. J. Vet. Res.* **19**, 610 (1958).

<sup>447</sup> N. Platonow and W. T. Oliver, *Res. Vet. Sci.* **1**, 371 (1960).

<sup>448</sup> N. T. Clare, *Psychopharmacol. Serv. Center Bull.* **2**, 44 (1962).

discovery in the 1950's of the exceptional pharmacological action of some *N*-substituted phenothiazines in the human organism, a tremendous volume of work has been devoted to the metabolism of this group of phenothiazine derivatives.

Metabolic changes of the phenothiazine drugs may involve either the side chain at position 10, or the heterocyclic ring, or both. The influence exerted by the side chain upon the chemical behavior of the phenothiazine ring is relatively slight, so that the products of metabolic modification undergone by a drug at the side chain may be further metabolized by reactions involving the ring in the same manner as the initial substances. The phenothiazine chemist is primarily interested in the chemical processes which take place *in vivo* in the ring.

Research on the metabolism of chlorpromazine is by far the most extensive; consequently, information about side chain modifications refer primarily to the dimethylaminopropyl residue. Among the metabolic products in man and animals, mono- and didesmethyl derivatives, either with or without ring modifications, are very often encountered (see, for example, refs. 449-459). Side chain demethylation has been observed also in promazine<sup>400</sup> and in thioridazine and E.T. 758,<sup>78</sup> where the methyl group is bound to a heterocyclic residue.

<sup>449</sup> N. P. Salzman and B. B. Brodie, *J. Pharmacol. Exptl. Therap.* **118**, 46 (1956).

<sup>450</sup> T. H. Lin, L. W. Reynolds, I. M. Rondish, and E. J. Van Loon, *Proc. Soc. Exptl. Biol. Med.* **102**, 602 (1959).

<sup>451</sup> V. Fishman and H. Goldenberg, *Proc. Soc. Exptl. Biol. Med.* **104**, 99 (1960).

<sup>452</sup> H. Goldenberg and V. Fishman, *Proc. Soc. Exptl. Biol. Med.* **108**, 178 (1961).

<sup>453</sup> V. Fishman, A. Heaton, H. Goldenberg, R. Burnett, and M. Rabinowitz, *Proc. Soc. Exptl. Biol. Med.* **109**, 548 (1962).

<sup>454</sup> J. J. Ross, Jr., T. L. Flanagan, and A. R. Marss, *J. Med. Pharm. Chem.* **5**, 1035 (1962).

<sup>455</sup> J. L. Emmerson and T. S. Miya, *J. Pharmacol. Exptl. Therap.* **137**, 148 (1962).

<sup>456</sup> V. Fishman and H. Goldenberg, *Proc. Soc. Exptl. Biol. Med.* **112**, 501 (1963).

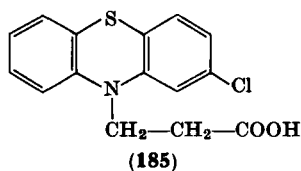
<sup>457</sup> A. H. Beckett, M. A. Beaven, and A. E. Robinson, *Biochem. Pharmacol.* **12**, 779 (1963).

<sup>458</sup> A. E. Robinson and V. H. Beaven, *J. Pharm. Pharmacol.* **16**, 342 (1964).

<sup>459</sup> A. E. Robinson, *J. Pharm. Pharmacol.* **18**, 19 (1966).

<sup>460</sup> S. S. Walkenstein and J. Seifter, *J. Pharmacol. Exptl. Therap.* **125**, 283 (1959).

Another reaction involving the side chain is *N*-oxidation, leading to *N*-oxides at the exocyclic nitrogen. Fishmann *et al.*<sup>452, 453</sup> have stated that in man this process is more important than oxidation at sulfur. It has been recently shown that oxidation at the end of the side chain may lead to the propionic acid (185) in the case of chlorpromazine.<sup>461</sup>



Although earlier reports suggested that there was no side chain fission during metabolism of phenothiazine drugs,<sup>16, 462, 463</sup> Fishman and Goldenberg<sup>464</sup> have isolated phenothiazine, *N*-unsubstituted phenothiazine-5-oxide (as the main product), and 3-hydroxyphenothiazine from human and canine urine, after administration of promazine; the corresponding 2-chloro derivatives were found in the case of chlorpromazine.

All of the metabolic changes undergone by the phenothiazine ring are oxidations, yielding either 5-oxides or 3-hydroxylated derivatives. There are two routes to these oxidized products, the first involving oxidation to the phenazathionium cation followed by hydrolysis of the latter, as shown in Sections IV,G,2 and IV,G,3, the second being based on the assumption that there are special enzymes which act upon the phenothiazine ring introducing the sulfoxide oxygen or the hydroxyl groups. The experimental evidence is not yet conclusive as to which is the most likely route.

<sup>461</sup> C. F. Rodriguez and D. E. Johnson, *Life Sci.* **5**, 1283 (1966).

<sup>462</sup> T. Berti and L. Cima, *Farmaco (Pavia), Ed. Sci.* **12**, 159 (1957); *Chem. Abstr.* **51**, 11578g (1957).

<sup>463</sup> C. J. Carr and G. J. Cosmides, *Proc. Intern. Union Physiol. Sci., Intern. 22nd Congr., Leiden, 1962* Vol. 1, Pt 1, p. 5. Excerpta Med. Found., Amsterdam, 1962.

<sup>464</sup> V. Fishman and H. Goldenberg, *J. Pharmacol. Exptl. Therap.* **150**, 122 (1965).



Forest and co-workers<sup>465, 466</sup> claimed that the first oxidation product *in vivo* (as *in vitro*) is the free radical produced by loss of an electron; they observed small amounts of a metabolite with the properties of a free radical in the urine of some patients treated with chlorpromazine.

The appearance of 5-oxides as elimination products is reported in many papers.<sup>78, 449, 451-453, 455, 456, 460, 464, 467-475</sup> It has been shown that oxidation at sulfur takes place in the liver.<sup>471</sup>

The possibility of an *in vivo* oxidation to the 5,5-dioxide has been considered. In the case of thioridazine, Zehnder *et al.*<sup>78</sup> found a 5,5-dioxide among the metabolization products of this drug. Salzman and Brodie<sup>449</sup> supposed that the 5,5-dioxide might be an advanced metabolic product of chlorpromazine, but this has been contested.<sup>451, 455</sup>

There are also cases when oxidation to the 5-oxide does not occur; thus, because of its amide structure, secergan is not so oxidized.<sup>476</sup> In the case of mepazine the small amount of sulfoxide isolated from biological fluids could be an artefact due to peroxides in the ether used for extraction.<sup>472</sup>

As far as ring hydroxylation is concerned, it appears that hydroxy groups are always introduced in position para to the heterocyclic nitrogen. Only monohydroxy derivatives are usually found. Nevertheless, 2-chlorothionol has been identified among the metabolic

<sup>465</sup> I. S. Forrest, F. M. Forrest, and M. Berger, *Biochim. Biophys. Acta* **29**, 441 (1958).

<sup>466</sup> I. S. Forrest and F. M. Forrest, *Exptl. Med. Surg.* **21**, 231 (1963).

<sup>467</sup> N. P. Salzman, N. C. Moran, and B. B. Brodie, *Nature* **176**, 1122 (1955).

<sup>468</sup> Y. Ogawa, A. Kawasaki, and K. Yamamoto, *Shionogi Kenkyusho Nempo* **8**, 229 (1958); *Chem. Abstr.* **53**, 7418h (1959).

<sup>469</sup> I. Hoffmann, O. Nieschultz, K. Pependiker, and E. Tauchert, *Arzneimittel-Forsch.* **9**, 133 (1959).

<sup>470</sup> L. G. Allgén, B. Jönson, A. Rappe, and R. Dahlbom, *Experientia* **15**, 318 (1959).

<sup>471</sup> J. R. Gillette and J. J. Kamm, *J. Pharmacol. Exptl. Therap.* **130**, 262 (1960).

<sup>472</sup> W. Block, *Arzneimittel-Forsch.* **11**, 266 (1961).

<sup>473</sup> J. R. Fouts, *Biochem. Biophys. Res. Commun.* **6**, 373 (1961).

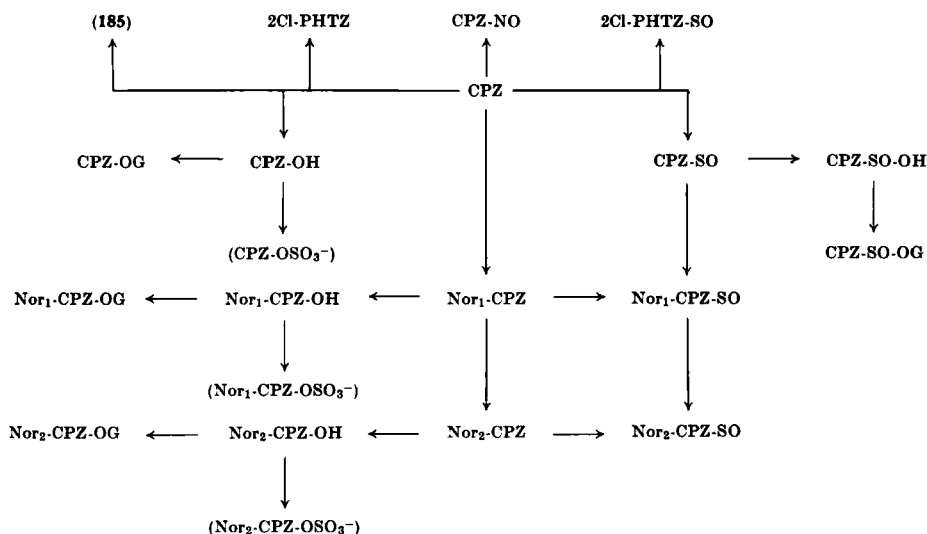
<sup>474</sup> J. R. Fouts, *Rept. Ross. Pediat. Res. Conf.* **41**, 54 (1962).

<sup>475</sup> M. Takesada, Y. Kakimoto, I. Sano, and J. Kaneko, *Nature* **199**, 203 (1963).

<sup>476</sup> L. G. Allgén, L. Eckman, L. Reio, and S. Ullberg, *Arch. Intern. Pharmacodyn.* **126**, 1 (1960).

products of chlorpromazine.<sup>464</sup> Monohydroxylation of this drug may occur in position 3 as well as in position 7.

The hydroxylated products derived from phenothiazine drugs are eliminated as glucuronides; the free hydroxy derivatives are obtained upon incubation with  $\beta$ -glucuronidase.<sup>78, 163, 450, 452, 456-458, 464, 477-482</sup>



*Key*

CPZ—Chlorpromazine  
 PHTZ—Phenothiazine  
 NO—N-Oxide  
 SO—5-Oxide  
 OH—3(7)-Hydroxy  
 OG—O-Glucuronide  
 OSO<sub>3</sub><sup>-</sup>—Sulfate ester  
 Nor<sub>1</sub>—Monodesmethyl  
 Nor<sub>2</sub>—Didesmethyl

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<sup>477</sup> M. Kikkawa, D. Sasaki, T. Iwasaki, and J. Ueda, *Osaka City Med. J.* **3**, 69 (1956); *Chem. Abstr.* **51**, 16892c (1957).

<sup>478</sup> G. Nadeau and G. Sobolewski, *Can. Med. Assoc. J.* **81**, 658 (1959).

<sup>479</sup> E. Hansson and C. G. Schmitterlow, *Arch. Intern. Pharmacodyn.* **131**, 309 (1961).

<sup>480</sup> K. Zehnder, F. Kalberer, and J. Rutschmann, *Biochem. Pharmacol.* **11**, 551 (1962).

<sup>481</sup> L. G. Allgén, L. Hellström, and C. I. Sant'Orp, *Acta Psychiat. Scand.* **39**, Suppl. 169, 1 (1963).

<sup>482</sup> A. H. Beckett, S. H. Curry, and A. G. Bolt, *J. Pharm. Pharmacol.* **16**, 500 (1964).

There is lack in agreement over the possibility of metabolic opening of the sulfide bridge in phenothiazines. Early workers using S<sup>35</sup>-labeled phenothiazines claimed that inorganic sulfates are found among the degradation products of promazine<sup>460</sup> and of chlorpromazine.<sup>483</sup> More recent work has indicated that there is no metabolic breaking of the phenothiazine ring *in vivo*.<sup>455, 463</sup>

The present knowledge of the metabolic pathways of phenothiazine drugs is depicted in Scheme 20 which is based on that presented by Beckett *et al.*<sup>484</sup>

Some of the metabolization products of phenothiazine drugs show a moderate pharmacological effect, and they may contribute a little to the action of the drug.<sup>449, 467-469, 485, 486</sup>

<sup>483</sup> J. Christensen and A. W. Wase, *Acta Pharmacol. Toxicol.* **12**, 81 (1956).

<sup>484</sup> A. H. Beckett, M. A. Beaven, and A. E. Robinson, *Psychopharmacol. Serv. Center Bull.* **2**, 42 (1962).

<sup>485</sup> J. D. Davidson, L. L. Terry, A. Sjoerdsma, and W. King, *J. Pharmacol. Exptl. Therap.* **121**, 8 (1957).

<sup>486</sup> H. S. Posner, E. Hearst, W. L. Taylor, and G. J. Cosmides, *J. Pharmacol. Exptl. Therap.* **137**, 84 (1962).

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